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Scope and applications of second generation palladium-catalyzed cycloalkenylation. Stereoselective total syntheses of isoiridomyrmecin, isodihydronepetalactone, and α-skytanthine

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Dedicated to Professor Gilbert Stork on the occasion of his 90th birthday

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α-Skytanthine

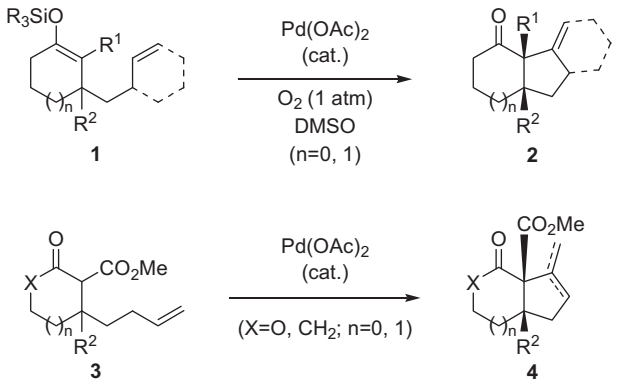
ABSTRACT

Functionalized bicyclo[3.2.1]octanes, -oxabicyclo-[4.3.0]nonanes, 3-azabicyclo[3.3.0]octanes, and 3-azabicyclo[4.3.0]nonanes were easily synthesized via a second generation palladium-catalyzed cycloalkenylation. Isoiridomyrmecin and isodihydronepetalactone, both of which feature a 3-oxabicyclo [4.3.0]nonane subunit, were stereoselectively synthesized via a second generation palladium-catalyzed cycloalkenylation as the key step. α-Skytanthine, a typical 3-azabicyclo[4.3.0]nonane alkaloid, was also constructed using the same catalytic cyclization protocol.

1. Introduction

Among catalytic carbon–carbon bond formation reactions,[1] the palladium-catalyzed cycloalkenylation (**1**→**2**) developed by us is one of the most efficient methodologies for constructing highly functionalized natural products.[2] The presence of a ketene silyl acetal moiety in a substrate, however, lowers the yield of the desired cyclization product due to instabilities in the ketene silyl acetal. To compensate for the disadvantages associated with palladium-catalyzed cycloalkenylation, we recently developed a second generation palladium-catalyzed cycloalkenylation method using olefinic keto or lactone esters (**3**→**4**) instead of silyl enol ethers (Scheme 1).[3]

Efforts to improve the second generation palladium-catalyzed cycloalkenylation reaction have proceeded with the goal of increasing the diversity of substrates and reaction products. In a prior report, we demonstrated the utility of the second generation palladium-catalyzed cycloalkenylation toward the synthesis of iridoid lactones, such as onikulactone[4] and mitsugashiwaklactone.[4] Here, we describe some notable results of the second generation palladium-catalyzed cycloalkenylation.



Scheme 1. Two different types of palladium-catalyzed cycloalkenylations.

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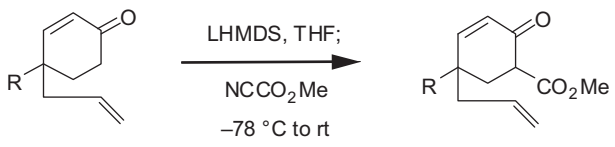
2. Results and discussion

2.1. Concise construction of the bicyclo[3.2.1]octane framework

The prevalence of the bicyclo[3.2.1]octane ring system as a structural subunit in bioactive natural products, such as gibberellins[5] and aphidicolin,[6] inspired the adaptation of our methodology to the synthesis of this ring system.

To demonstrate the feasibility of this protocol, we initially synthesized the requisite keto esters **6** from **5**, as depicted in Scheme 2. Namely, compound **5** was treated with methyl cyanoformate at −78 °C in THF in the presence of lithium hexamethyldisilazide (LHMDS) to provide the keto ester **6** in moderate yield.



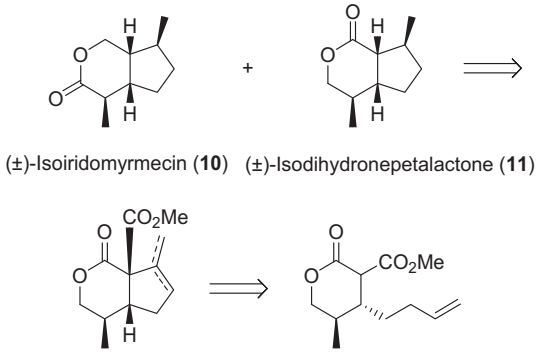
5a (R=H) **6a** (55%)
5b (R=Me) **6b** (38%)
5c (R=CH_2OMOM) **6c** (86%)
5d (R=CH_2CH_2OMOM) **6d** (57%)

Scheme 2. Preparation of **6** from **5**.

With substrates **6** in hand, the second generation palladium-catalyzed cycloalkenylation of **6** was examined. The results of these tests are summarized in Table 1. Subjection of compound **6a** to the second generation palladium-catalyzed cycloalkenylation produced the desired cyclization product **7**, together with small amounts of the phenol derivative **9** (entries 1–3). It should be noted that the presence of 1 atm oxygen may not be required for the cyclization process (entry 3). Substrate **6b**, which includes a methyl group at the angular position, produced better yields (entries 4–8) than **6c** and **6d**, each of which included a bulky substituent group at the angular position, which decreased the yield of the corresponding cyclization products (entries 9–14).

2.2. Diastereoselective total syntheses of two types of iridoids

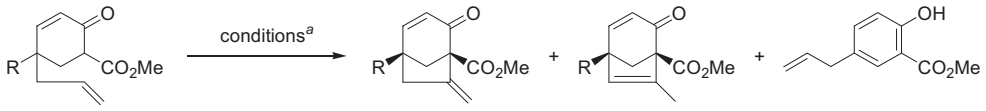
With the goal of constructing an iridoid skeleton, we initiated the total syntheses of isoiridomyrmecin (**10**), isolated from *Iridomyrmex nitidus*,[7] and isodihydronepetalactone (**11**), isolated from *Actinidia polygama* in 1965,[8] using the second generation palladium-catalyzed cycloalkenylation. Our retrosynthetic plan is outlined in Scheme 3. We envisaged that both natural products (**10** and **11**) could be synthesized by functional group transformations of the bicyclic compound **12**, which could be constructed from the trans substituted olefinic lactone **13** via second generation palladium-catalyzed cycloalkenylation.



Scheme 3. Retrosynthetic analysis of (±)-isoiridomyrmecin (**10**) and (±)-isodihydronepetalactone (**11**).

Conjugate addition of the homoallyl magnesium bromide to **14** (94%), followed by methoxycarbonylation of **15**, afforded the lactone ester **13** in 96% yield as a 3:1 mixture of diastereoisomers (Scheme 4). The second generation palladium-catalyzed cycloalkenylation was performed under a variety of conditions, as shown in Table 2. Subjection of **13** to the catalytic cyclization at 45 °C in DMSO in the presence of 5 mol % $Pd(OAc)_2$ and 20 mol % LiBr furnished the desired cyclization product **12** in 68% yield as a mixture of olefin isomers (entry 6). It should be noted that compound **17** was formed under these reaction conditions (entries 4–6). Investigations into the role of lithium

Table 1
Preparation of bicyclo[3.2.1]octanes by second generation palladium-catalyzed cycloalkenylation

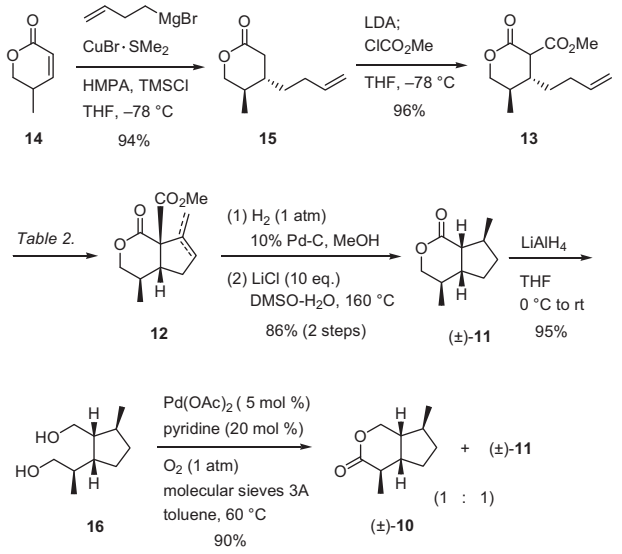


6 **7** **8** **9**

Entry	Substrate	$Pd(OAc)_2$ (mol %)	Atmosphere[b]	Temperature (°C)	Time (h)	Yield (%)		
						7	**8**	**9**
1	**6a** (R=H)	10	O_2	rt	60	58	0	12
2		5	O_2	rt	72	48	0	12
3		10	Air	rt	70	52	0	6
4	**6b** (R=Me)	10	O_2	rt	67	63	Trace	—
5		10	O_2	80	13	72	7	—
6		5	O_2	80	11	76	3	—
7		2	O_2	80	26	72	6	—
8		10	Air	80	20	70	5	—
9	**6c** (R=CH_2OMOM)	10	O_2	rt	67	50	Trace	—
10		10	O_2	80	6	66	5	—
11		10	Air	80	12	67	3	—
12	**6d** (R=$(CH_2)_2OMOM$)	10	O_2	rt	84	53	6	—
13		10	O_2	80	5	55	6	—
14		10	Air	rt	132	43	6	—

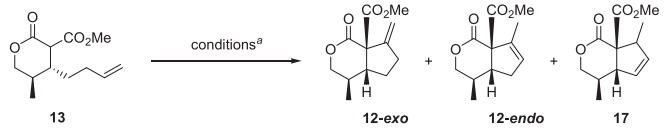
[a] All reactions were run in DMSO.
[b] Each reaction was conducted under 1 atm of oxygen or under air atmosphere.

halides are underway. $^1H-^1H$ COSY studies of **17a** and **17b** enabled all protons of each compound to be assigned, and the relative stereochemistries were established on the basis of NOE correlations, as depicted in Fig. 1. Without separation of the *exo* and *endo* isomers, **12** was reduced in the presence of 10% Pd/C under a hydrogen atmosphere (1 atm) to provide the corresponding lactone ester, which was subjected to the Krapcho reaction to yield (±)-isodihydronepatalactone (**11**) in 86% total yield. The ^1H and ^{13}C NMR spectra of the synthetic **11** were identical to those previously reported.[9]



Scheme 4. Diastereoselective total synthesis of (±)-isoiridomyrmecin (**10**) and (±)-isodihydronepetalactone (**11**).

Table 2
Second generation palladium-catalyzed cycloalkenylation of olefinic lactone ester **13**



Entry	$Pd(OAc)_2$ (mol %)	Additive	Solvent	Time (h)	Yield (%)		
					12-*exo*	**12**-*endo*	**17**
1	100	—	DMSO	13	60	8	0
2	10	—	DMSO	38	30	7	0
3	10	DMSO (5 equiv)	Toluene	84	34	17	Trace
4	10	LiCl (2 equiv)	DMSO	68	5	31	55 (α/β=1.6:1)
5	5	LiCl (20 mol %)	DMSO	12	11	46	34 (α/β=3.2:1)
6	5	LiBr (20 mol %)	DMSO	12	17	51	25 (α/β=4.3:1)

[a] All reactions were carried out under 1 atm oxygen at 45 °C.

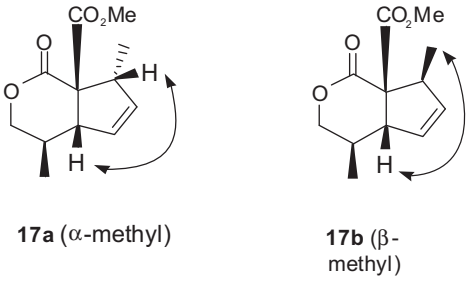
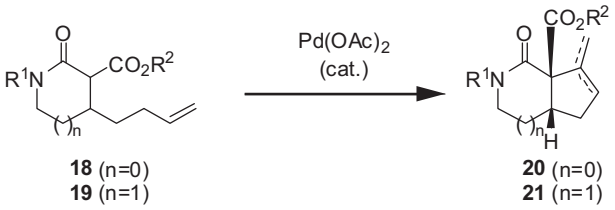


Fig. 1. Significant NOESY correlations in **17a** and **17b**.

To assemble (±)-isoiridomyrmecin (**10**), compound **11** was reduced with $LiAlH_4$ to give the diol **16**,[10] which was subsequently oxidized with catalytic $Pd(OAc)_2$ in the presence of pyridine and molecular sieves 3 Å[11] to produce a 1:1 mixture of the desired products, **10** and **11**, in 90% yield. The natural products were separated by HPLC, and the ^1H and ^{13}C NMR spectra of the synthetic **10** were identical to those provided by Professor Tsunoda.[12]

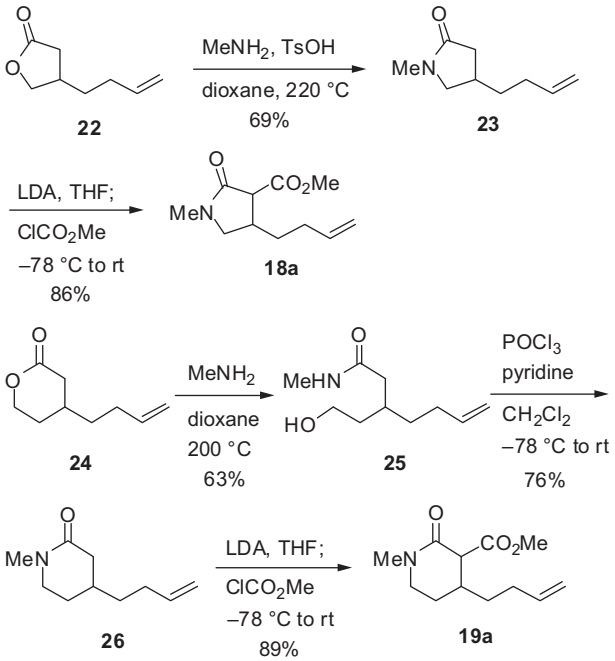
2.3. Efficient synthesis of 3-azabicyclo[3.3.0]octanes and 3-azabicyclo[4.3.0]nonanes

3-Azabicyclo[3.3.0]octanes and 3-azabicyclo[4.3.0]nonanes present major classes of nitrogen-containing heterocycles, which display an increasingly important role in drug discovery. These compounds are structural units found in a vast range of natural products, such as dendrobine[13] and skytanthines.[14] We sought to extend our protocol to construct these ring systems (Scheme 5).



Scheme 5. Second generation palladium-catalyzed cycloalkenylation of olefinic lactam esters **18** and **19**.

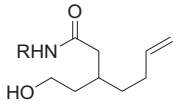
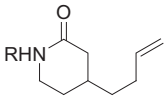
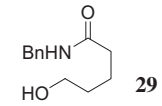
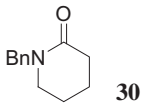
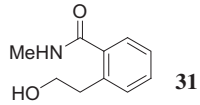
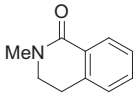
To test the possibility of the transformations **18**→**20** and **19**→**21**, the requisite substrates **18** and **19** were prepared (Scheme 6). Heating γ-lactone **22** with methylamine at 220 °C in dioxane in the presence of TsOH using a stainless autoclave directly produced γ-lactam **23** in 69% yield (Scheme 6). Methoxycarbonylation of **23** was next conducted using methyl chloroformate in THF in the presence of LDA to give the desired γ-lactam ester **18a** in 86% yield. In contrast with the above result, the reaction of δ-lactone **24** with methylamine at 200 °C in a stainless autoclave afforded the corresponding amide alcohol **25** (63%), which was converted to the δ-lactam **26** in 76% yield using $POCl_3$. Finally, methoxycarbonylation of **26** was performed in the manner described above to furnish the δ-lactam ester **19a**.



Scheme 6. Synthesis of lactam esters **18a** and **19a**.

At this stage, we examined the transformation from the amide alcohol to the corresponding δ-lactam under a variety of conditions, and some results are summarized in Table 3.

Table 3
Lactam formation from amide alcohols

Entry	Substrate	Conditions	Product	Yield (%)
1	 **25** (R=Me)	CMBP[a]	 **26** (R=Me)	24
2		$POCl_3$, pyridine[b]		76
3	**27** (R=Bn)	$POCl_3$, pyridine[b]	**28** (R=Bn)	60
4	 **29**	CMBP[c]	 **30**	0
5		$POCl_3$, pyridine[b]		22
6	 **31**	CMBP[c]	 **32**	9
7		$POCl_3$, pyridine[b]		57

[a] Reaction was run at 100 °C in benzene.
[b] Reactions were run at −78 °C to at rt in CH_2Cl_2.
[c] Reactions were run at rt in benzene.

To the best of our knowledge, the use of $POCl_3$ in a lactam synthesis, as described above, is rare.[17]

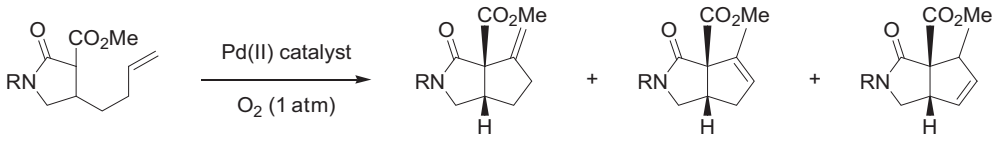
With the γ-lactam esters **18** and the δ-lactam esters **19** in hand, second generation palladium-catalyzed cycloalkenylations of **18** and **19** were investigated. To optimize the reaction parameters, we focused on substrate **18** and varied the palladium source, solvent, additive, and reaction temperature as shown in Table 4. $Pd(OAc)_2$ was found to be the most suitable catalyst for achieving catalytic cyclization (entry 5). $Pd(OCOCF_3)_2$ gave the desired cyclization products **33c** and **34c** as a mixture in 64% yield, however, neither $Pd(acac)_2$ nor $PdCl_2(MeCN)_2$ provided the desired compounds (entries 9 and 10). Unlike the palladium-catalyzed cycloalkenylation of the olefinic keto and lactone esters, the reaction of **18c** proceeded at 45 °C in toluene in the presence of 5 equiv of DMSO, leading to **33c** and **34c** in 89% yield as a 2.9:1 mixture (entry 5).

With the optimized conditions in hand, we continued to examine the scope of the reaction (Table 5). The *N*-methyl substrate **18a** was converted to **33a** and **34a** in 76% yield as a 2.6:1 mixture (entry 1). Compound **18b**, which includes a benzyl substituent on the nitrogen, afforded **33b** and **34b** in 84% yield as a 2:1 mixture (entry 2). Substrate **18c** gave the best result (entry 3), indicating that the tertiary butyl group was a suitable protecting group for the lactam moiety in **18**. The bulkiness of the ester moiety in **18** did not affect the cyclization yield (entries 4 and 5).

We next investigated the reaction of the olefinic δ-lactam **19**. The *N*-methyl substrate **19a** gave the desired cyclization products **36a** and **37a** in moderate yield as a 1:1.6 mixture (entry 6); however, the yield slightly decreased for the reaction with the *N*-benzyl substrate **19b** (entry 7). The *N*-tertiary butyl substituent proved to be ineffective (entry 8). Changing the ester group from methyl to benzyl improved the yield (entry 9). The *N*-methyl isopropyl ester **19e** provided **36e** and **37e** in good yield (entry 10).

The relative stereochemistries of compounds **33e** and **36e** were established on the basis of NOE correlations, as shown in Fig. 2.

Table 4
Second generation palladium-catalyzed cycloalkenylation of γ-lactam esters **18**



18 **33** **34** **35**

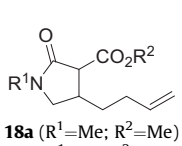
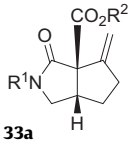
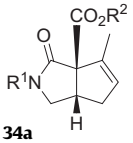
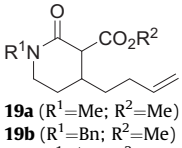
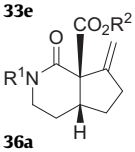
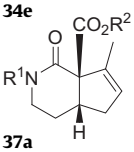
Entry	Substrate	Pd(II) catalyst (10 mol %)	Addtives (5 equiv)	Temperature (°C)	Solvent	Time (h)	Yield (%)		
							33	**34**	**35**
1	**18a** (R=Me)	$Pd(OAc)_2$	—	45	DMSO	94	39	13	—
2			DMSO	45	Toluene	24	34	11	—
3			DMSO	45	Toluene	94	55	21	—
4	**18c** (R=^{t}Bu)	$Pd(OAc)_2$	—	45	DMSO	94	48	13	0
5			DMSO	45	Toluene	94	66	23	0
6			DMSO, MS 3 Å	45	Toluene	92	30	0	0
7			DMSO, MS 3 Å	80	Toluene	20	21	0	0
8		$Pd(OCOCF_3)_2$	DMSO	45	Toluene	94	16	48	14
9		$Pd(acac)_2$	DMSO	45	Toluene	94	0	0	0
10		$PdCl_2(MeCN)_2$	DMSO	45	Toluene	94	0	0	0

Generally, amide alcohols could be converted to the corresponding δ-lactam under the Mitsunobu conditions[15] or modified Mitsunobu conditions.[16] Because the Mitsunobu conditions were not suitable for **25**, compound **25** was subjected to modified Mitsunobu conditions using cyanomethyl-enetributylphosphorane (CMBP) to provide **26** in 24% yield (entry 1). On the other hand, the reaction of **25** with $POCl_3$ at −78 °C to rt gave rise to **26** in 76% yield (entry 2). Substrate **27**, which includes a benzyl substituent on the nitrogen, furnished **28** in 60% yield (entry 3), although the cyclization product **30** was obtained using $POCl_3$ in only 22% yield (entry 5). It should be noted that the reaction of **29** with CMBP did not give the cyclization product **30**. This procedure proved to be effective for the synthesis of 3,4-dihydroisoquinolinone **32**, and the desired product **32** was obtained in 57% yield using $POCl_3$ (entry 7).

2.4. Diastereoselective total synthesis of α-skytanthine (38)

To expand our methodology, we undertook the stereoselective total synthesis of (±)-α-skytanthine (**38**).[18] Scheme 7 shows the retrosynthetic analysis. We expected that the target molecule could be obtained through a series of functional group manipulations

Table 5
Second generation palladium-catalyzed cycloalkenylation of olefinic lactam esters **18** and **19**[a]

Entry	Substrate	Product		Yield (%)
				
1	**18a** (R^1=Me; R^2=Me)	**33a**	**34a**	76 (2.6:1)
2	**18b** (R^1=Bn; R^2=Me)	**33b**	**34b**	84 (2:1)
3	**18c** (R^1=^{t}Bu; R^2=Me)	**33c**	**34c**	89 (2.9:1)
4	**18d** (R^1=^{t}Bu; R^2=Bn)	**33d**	**34d**	88 (5.5:1)
5	**18e** (R^1=^{t}Bu; R^2=^{i}Pr)	**33e**	**34e**	83 (8:1)
				
6	**19a** (R^1=Me; R^2=Me)	**36a**	**37a**	68 (1:1.6)
7	**19b** (R^1=Bn; R^2=Me)	**36b**	**37b**	61 (1:1.3)
8	**19c** (R^1=^{t}Bu; R^2=Me)	**36c**	**37c**	24 (1.2:1)
9	**19d** (R^1=Me; R^2=Bn)	**36d**	**37d**	75 (1:1.2)
10	**19e** (R^1=Me; R^2=^{i}Pr)	**36e**	**37e**	76 (1:1.4)

Values in parentheses refer to ratio of cyclization products determined by ^{1}H NMR spectra.
[a] All reactions were run at 45 °C in toluene in the presence of 10 mol % of $Pd(OAc)_2$ and 5 equiv of DMSO for 94 h under 1 atm of oxygen.

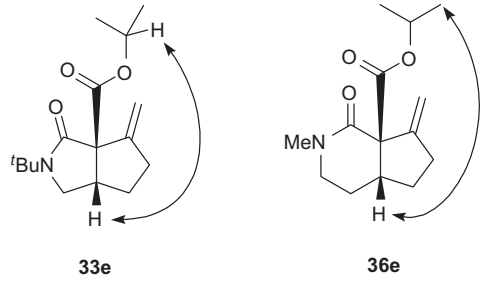
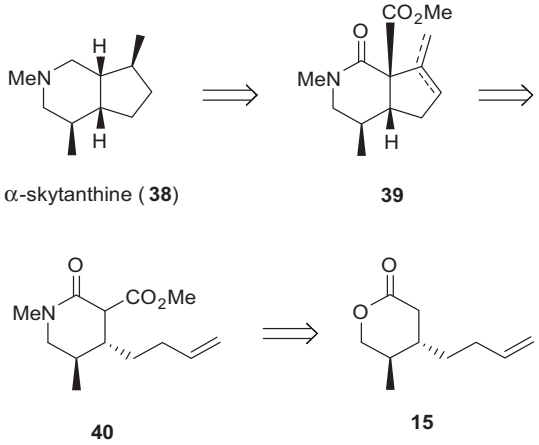


Fig. 2. Significant NOESY correlations in **33e** and **36e**.

from 3-azabicyclo[4.3.0]nonane **39**, which could be constructed from **40** via the second generation palladium-catalyzed cycloalkenylation process. Substrate **40** could be synthesized from the lactone **15** by lactam formation followed by methoxycarbonylation.



Scheme 7. Retrosynthetic analysis of (±)-α-skytanthine (**38**).

Compound **15** was transformed into the lactam **42** through the amide alcohol **41** in a good overall yield, as described earlier (Scheme 8). After introduction of a methoxycarbonyl moiety on **42**, the desired **40** was obtained in 91% yield. We next investigated the second generation palladium-catalyzed cycloalkenylation of the lactam ester **40** under a variety of conditions, as listed in Table 6. Although the reaction did not proceed at rt at all (entry 2), the desired cyclization products **39**-*exo* and **39**-*endo* were obtained in good yield when the reaction was performed at 45 °C in toluene in the presence of 10 mol % $Pd(OAc)_2$ with additives (entries 3–6). The best result, a 70% total yield, was obtained under the reaction conditions listed in entry 5. Without separating the *exo* and *endo* isomers, **39** was subjected to hydrogenation in the presence of 10% Pd/C to furnish the saturated lactam ester **43** as a single stereoisomer. In this case, reduction occurred from the side opposite the angular ester group. The Krapcho reaction of **43** led to the lactam **44** as the sole product. Finally, **44** was converted to (±)-α-skytanthine (**38**) in 88% yield via $LiAlH_4$ reduction. The spectral data gathered from the synthetic **38** were identical to those gathered from an authentic sample provided by Professor Honda.[18e]

3. Conclusion

Functionalized bicyclo[3.2.1]octanes, 3-oxabicyclo[4.3.0]nonanes, 3-azabicyclo[3.3.0]octanes, and 3-azabicyclo[4.3.0]nonanes were easily synthesized by a second generation palladium-catalyzed cycloalkenylation. In addition, α-skytanthine, a typical 3-azabicyclo[4.3.0]nonane alkaloid, was stereoselectively constructed by applying the above catalytic cyclization protocol. In sharp contrast to Conia-ene reactions,[19] the present catalytic reaction proceeds smoothly without any Lewis acids.

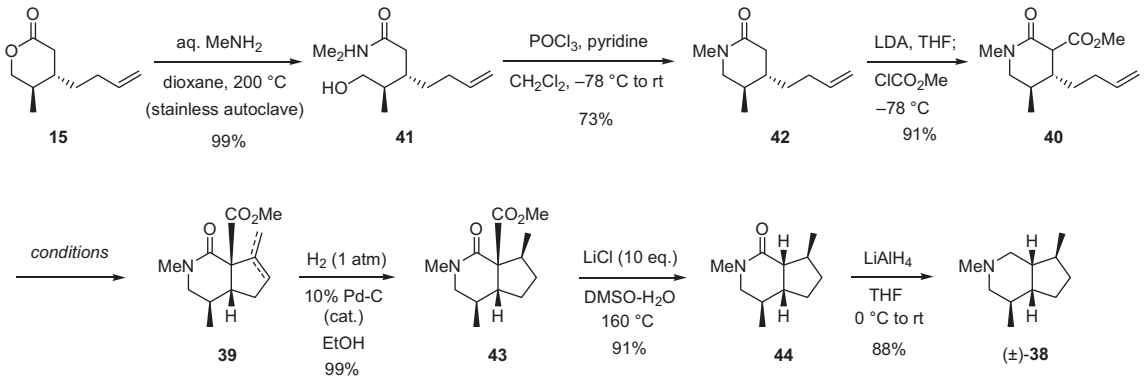
4. Experimental section

4.1. General information

Unless otherwise noted, all reactions were performed in oven-dried glassware, sealed with a rubber septum under an atmosphere of argon. Anhydrous THF and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. Pyridine, $^iPr_2NH$ and TMSCl were distilled from CaH_2 prior to use. Toluene and benzene were distilled from P_2O_5. DMSO and HMPA were distilled from CaH_2 under reduced pressure. Unless otherwise mentioned, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was carried out using Cica 60 N (spherical, neutral/40–50 μm) silica gel. IR spectra were measured on an SHIMADZU FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on Varian 400 MR (400 MHz) spectrometers with $CHCl_3$ (δ 7.26) as an internal standard. ^{13}C NMR spectra were recorded on Varian 400 MR (100 MHz) spectrometer with $CHCl_3$ (δ 77.16) as an internal standard. Mass spectra were recorded on JEOL JMS-700 spectrometers.

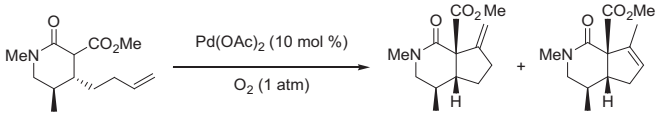
4.2. Experimental procedures and characterization of new compounds

*4.2.1. Methyl 5-(2-propenyl)-2-oxo-3-cyclohexene-1-carboxylate (**6a**).* A solution of **5a** (1.00 g, 7.34 mmol) in THF (10 mL) was added dropwise to a solution of LHMDS, prepared from hexamethyldisilazane (1.60 mL, 7.63 mmol) and *n*-butyllithium (1.69 M in hexane, 4.4 mL, 7.4 mmol) in THF (20 mL), at −78 °C. After 1 h, methyl cyanoformate (0.60 mL, 7.5 mmol) was added dropwise. After 1 h, the mixture was treated with water and extracted with hexane/EtOAc (1:1 v/v, three times). The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to



Scheme 8. Total synthesis of (±)-α-skytanthine (**38**).

Table 6
Second generation palladium-catalyzed cycloalkenylation of olefinic lactam ester **40**



Entry	Additive	Solvent	Temperature (°C)	Time (h)	Yield (%)	Ratio[a] **39**-*exo*/ **39**-*endo*
1	None	DMSO	45	43	26	1:1.2
2	DMSO (3 equiv)	Toluene	rt	85	0	—
3	DMSO (3 equiv)	Toluene	45	44	55	1:1.9
4	DMSO (5 equiv)	Toluene	45	94	65	1:1.2
5	DMSO (5 equiv), MS 3 Å	Toluene	45	86	70	1:1.1
6	DMSO (10 equiv), MS 3 Å	Toluene	45	64	57	1:1.1

[a] The ratios of cyclization products were determined by ^{1}H NMR spectrum.

flash chromatography (hexane/EtOAc 4:1 v/v) to afford **6a** (786.2 mg, 55%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92–6.85 (1H, m), 6.07–6.02 (1H, m), 5.82–5.72 (1H, m), 5.16–5.09 (2H, m), 3.78 (2H, s), 3.73 (1H, s), 3.47 (0.33H, dd, *J* 5.6, 5.6 Hz), 3.43 (0.67H, dd, *J* 14.4, 4.8 Hz), 2.75–2.45 (1.67H, m), 2.28–2.22 (2H, m), 2.06 (0.67H, ddd, *J* 14.4, 13.6, 11.6 Hz), 1.94 (0.33H, ddd, *J* 13.6, 8.4, 5.2 Hz); IR (neat) 1743, 1682, 1237, 1165 cm^{-1}; HRMS (EI) *m*/*z* 194 (M)$^+$ calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0941.

*4.2.2. Methyl 5-methyl-2-oxo-5-(2-propenyl)-3-cyclohexene-1-carboxylate (**6b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (0.6H, br s), 6.71 (0.2H, dd, *J* 10.0, 2.0 Hz), 6.68 (0.2H, dd, *J* 10.2, 2.0 Hz), 6.05 (0.6H, d, *J* 10.0 Hz), 5.95 (0.2H, d, *J* 10.2 Hz), 5.93 (0.2H, d, *J* 10.0 Hz), 5.89 (0.6H, d, *J* 10.0 Hz), 5.84–5.71 (1H, m), 5.19–5.00 (2H, m), 3.79–3.76 (3H, m), 3.60 (0.2H, dd, *J* 4.8, 2.4 Hz), 3.57 (0.2H, dd, *J* 5.2, 2.0 Hz), 2.46–2.04 (4H, m), 1.20 (0.6H, s), 1.16 (0.6H, s), 1.03 (1.8H, s); IR (neat) 1746, 1684, 1659, 1443, 1361, 1304, 1239 cm^{-1}; HRMS (EI) *m*/*z* 208 (M)$^+$ calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1100.

*4.2.3. Methyl 5-(methoxymethoxymethyl)-2-oxo-5-(2-propenyl)-3-cyclohexene-1-carboxylate (**6c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (0.4H, br s), 6.82 (0.3H, dd, *J* 10.0, 2.0 Hz), 6.71 (0.3H, dd, *J* 10.0, 2.0 Hz), 6.13–5.98 (1.6H, m), 5.84–5.69 (1H, m), 5.20–5.02 (2H, m), 4.63–4.58 (2H, m), 3.82–3.76 (3.3H, m), 3.66–3.45 (1.7H, m), 3.40–3.33 (3.6H, m), 2.48–2.03 (4H, m); IR (neat) 1744, 1661, 1240, 1153, 1109, 1042 cm^{-1}; HRMS (EI) *m*/*z* 268 (M)$^+$ calcd for $C_{14}H_{20}O_5$ 268.1311, found 268.1309.

*4.2.4. Methyl 5-(2-methoxymethoxyethyl)-2-oxo-5-(2-propenyl)-3-cyclohexene-1-carboxylate (**6d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (0.6H, br s), 6.80 (0.2H, dd, *J* 10.0, 2.0 Hz), 6.77 (0.2H, dd, *J* 10.0, 2.0 Hz), 6.11–5.92 (1.6H, m), 5.82–5.69 (1H, m), 5.20–5.01 (2H, m), 4.61–4.56 (2H, m), 3.79–3.76 (3H, m), 3.69–3.51 (2H, m), 3.38–3.34 (3.4H, m), 2.45–2.00 (4H, m), 1.94–1.64 (2H, m); IR (neat) 1745, 1683, 1238, 1152, 1109, 1045 cm^{-1}; HRMS (EI) *m*/*z* 282 (M)$^+$ calcd for $C_{15}H_{22}O_5$ 282.1467, found 282.1468.

4.2.5. Methyl (1S,5R*)-7-methylene-2-oxobicyclo[3.2.1]oct-3-ene-1-carboxylate (**7a**).* To a solution of **6a** (34.6 mg, 0.178 mmol) in DMSO (3 mL) was added $Pd(OAc)_2$ (4.0 mg, 0.018 mmol). The mixture was stirred under 1 atm of oxygen. After 60 h, the mixture was treated with aqueous NaCl solution, extracted with hexane/EtOAc (1:1 v/v, three times). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 4:1 v/v) to provide **7a** (20.0 mg, 58%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17(1H, ddd, *J* 9.6, 6.8, 1.6 Hz), 5.89–5.87 (1H, m), 5.85 (1H, d, *J* 9.6 Hz), 5.37–5.35(1H, m), 3.79 (3H, s), 2.95 (1H, ddd, *J* 6.0, 6.0, 4.0 Hz), 2.79 (1H, dddd, *J* 15.2, 5.6, 2.8, 2.8 Hz), 2.51 (1H, dd, *J* 11.6, 2.8 Hz), 2.39 (1H, ddd, *J* 15.2, 1.2, 1.2 Hz), 2.21 (1H, ddd, *J* 11.6, 4.0, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 169.8, 154.4, 141.2, 126.5, 117.2, 67.2, 52.4, 44.2, 37.7, 34.8; IR (neat) 1748, 1683, 1260, 1069 cm^{-1}; HRMS (EI) *m*/*z* 192 (M)$^+$ calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0790.

*4.2.6. Methyl 5-(2-propenyl)-2-hydroxybenzoate (**9**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (1H, s), 7.64 (1H, d, *J* 2.4 Hz), 7.29 (1H, dd, *J* 8.4, 2.4 Hz), 6.92 (1H, d, *J* 8.4 Hz), 5.93 (1H, ddt, *J* 16.8, 10.4, 6.4 Hz), 5.10–5.03 (2H, m), 3.94 (3H, s), 3.32 (2H, d, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 160.2, 137.4, 136.4, 130.8, 129.5, 117.7, 116.2, 112.2, 52.4, 39.3; IR (neat) 1682, 1490, 1442, 1297, 1210 cm^{-1}; HRMS (EI) *m*/*z* 192 (M)$^+$ calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0790.

4.2.7. Methyl (1S,5R*)-5-methyl-7-methylene-2-oxobicyclo-[3.2.1]oct-3-ene-1-carboxylate (**7b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, dd, *J* 9.6, 2.4 Hz), 5.83 (1H, d, *J* 9.6 Hz), 5.82–5.80 (1H, m), 5.30–5.28 (1H, m), 3.79 (3H, s), 2.54 (1H, ddd, *J* 15.6, 2.4, 2.4 Hz), 2.44–2.37 (2H, m), 2.10 (1H, dd, *J* 11.6, 2.0 Hz), 1.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 169.7, 158.9, 142.5, 125.6, 116.6, 67.8, 52.4, 50.3, 45.1, 40.8, 23.4; IR (neat) 1749, 1686, 1281, 1240, 1049 cm^{-1}; HRMS (EI) *m*/*z* 206 (M)$^+$ calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0940.

4.2.8. Methyl (1S,5R*)-5,7-dimethyl-2-oxobicyclo[3.2.1]octa-3,6-diene-1-carboxylate (**8b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (1H,

dd, *J* 9.6, 2.0 Hz), 6.08–6.06 (1H, m), 5.38 (1H, d, *J* 9.6 Hz), 3.77 (3H, s), 2.89 (1H, d, *J* 10.0 Hz), 2.58 (1H, dd, *J* 10.0, 2.0 Hz), 1.09 (3H, d, *J* 1.6 Hz), 1.33 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 170.0, 161.2, 143.8, 141.3, 121.3, 71.7, 59.8, 52.1, 46.3, 21.7, 14.8; IR (neat) 1747, 1682, 1280, 1170, 1049 cm^{-1}; HRMS (EI) *m*/*z* 206 (M)$^+$ calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0935.

4.2.9. Methyl (1S,5S*)-5-(methoxymethoxymethyl)-7-methylene-2-oxobicyclo[3.2.1]oct-3-ene-1-carboxylate (**7c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dd, *J* 9.6, 2.4 Hz), 5.91 (1H, d, *J* 9.6 Hz), 5.87–5.85 (1H, m), 5.34–5.31 (1H, m), 4.67 (2H, s), 3.80 (3H, s), 3.67 (1H, d, *J* 9.6 Hz), 3.64 (1H, d, *J* 9.6 Hz), 3.39 (3H, s), 2.66 (1H, ddd, *J* 15.2, 2.4, 2.4 Hz), 2.50–2.40 (2H, m), 2.16 (1H, dd, *J* 11.6, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 169.6, 155.2, 141.3, 126.4, 117.1, 96.8, 71.6, 67.3, 55.6, 52.5, 46.2, 45.2, 40.9; IR (neat) 1748, 1687, 1234, 1151, 1110, 1040 cm^{-1}; HRMS (EI) *m*/*z* 266 (M)$^+$ calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1154.

4.2.10. Methyl (1S,5S*)-5-(methoxymethoxymethyl)-7-methyl-2-oxobicyclo[3.2.1]octa-3,6-diene-1-carboxylate (**8c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, dd, *J* 9.6, 1.6 Hz), 6.16–6.13 (1H, m), 5.46 (1H, d, *J* 9.6 Hz), 4.67 (2H, s), 3.77 (3H, s), 3.66 (1H, d, *J* 9.6 Hz), 3.63 (1H, d, *J* 9.6 Hz), 3.39 (3H, s), 2.91 (1H, d, *J* 10.0 Hz), 2.68 (1H, dd, *J* 10.0, 1.6 Hz), 1.93 (3H, d, *J* 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 169.7, 157.0, 142.4, 139.8, 122.0, 96.8, 71.2, 69.8, 55.5, 52.2, 50.9, 15.0; IR (neat) 1747, 1683, 1111, 1042 cm^{-1}; HRMS (EI) *m*/*z* 266 (M)$^+$ calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1154.

4.2.11. Methyl (1S,5R*)-5-(2-methoxymethoxyethyl)-7-ethylene-2-oxobicyclo[3.2.1]oct-3-ene-1-carboxylate (**7d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, dd, *J* 9.6, 2.0 Hz), 5.85 (1H, d, *J* 9.6 Hz), 5.84–5.82 (1H, m), 5.31–5.29 (1H, m), 4.61 (2H, s), 3.79 (3H, s), 3.67 (2H, td, *J* 6.4, 1.6 Hz), 3.35 (3H, s), 2.61 (1H, ddd, *J* 15.2, 2.4, 2.4 Hz), 2.52–2.42 (2H, m), 2.09 (1H, dd, *J* 11.6, 2.0 Hz), 2.01 (1H, dt, *J* 14.4, 6.4 Hz), 1.91 (1H, dt, *J* 14.4, 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 169.7, 157.6, 141.7, 125.8, 116.8, 96.7, 67.5, 64.9, 55.6, 52.5, 48.5, 44.0, 43.4, 37.2; IR (neat) 2950, 1747, 1683, 1281, 1232, 1150, 1107, 1047 cm^{-1}; HRMS (EI) *m*/*z* 280 (M)$^+$ calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1315.

4.2.12. Methyl (1S,5S*)-5-(2-methoxymethoxyethyl)-7-methyl-2-oxobicyclo[3.2.1]octa-3,6-diene-1-carboxylate (**8d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, dd, *J* 9.6, 2.0 Hz), 6.14–6.12 (1H, m), 5.39 (1H, d, *J* 9.6 Hz), 4.61 (2H, s), 3.77 (3H, s), 3.66 (2H, t, *J* 6.4 Hz), 3.35 (3H, s), 2.91 (1H, d, *J* 10.0 Hz), 2.64 (1H, dd, *J* 10.0, 2.0 Hz), 2.01 (1H, dt, *J* 14.4, 6.4 Hz), 1.92 (1H, dt, *J* 14.4, 6.4 Hz), 1.91 (3H, d, *J* 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 169.9, 160.0, 142.4, 141.4, 121.2, 96.7, 71.5, 64.6, 57.6, 55.6, 52.1, 48.9, 35.0, 14.9; IR (neat) 1747, 1682, 1110, 1048 cm^{-1}; HRMS (EI) *m*/*z* 280 (M)$^+$ calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1315.

4.2.13. (4S,5R*)-4-(3-Butenyl)-tetrahydro-5-methylpyran-2-one (**15**).* Copper(I) bromide–dimethyl sulfide complex (172 mg, 0.837 mmol) and HMPA (3.5 mL) were added to a solution of 3-butenylmagnesium bromide, prepared from magnesium turnings (299 mg, 12.3 mmol) and 4-bromo-1-butene (1.25 mL, 12.3 mmol) in THF (25 mL), at −78 °C. After 30 min, a mixture of **14** (889 mg, 7.93 mmol) and TMSCl (2.2 mL, 17 mmol) in THF (8 mL) was added dropwise. After 1.5 h, the mixture was treated with 10% aqueous NH_4Cl solution, and extracted with hexane/EtOAc (3:1 v/v, three times). The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 3:1 v/v) to provide **15** (1.259 g, 94%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, ddt, *J* 17.2, 10.0, 6.8 Hz), 5.04 (1H, ddt, *J* 17.2, 1.6, 1.6 Hz), 5.00 (1H, ddt, *J* 10.0, 1.6, 1.6 Hz), 4.26 (1H, dd, *J* 11.2, 4.8 Hz), 3.88 (1H, dd, *J* 11.2, 9.2 Hz), 2.70 (1H, dd, *J* 17.2, 6.0 Hz), 2.20–2.10 (1H, m), 2.19 (1H, dd, *J* 17.2, 8.8 Hz), 2.07–1.96 (1H, m), 1.78–1.57 (3H, m), 1.36–1.28 (1H, m), 1.00 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 137.7, 115.5, 73.5, 37.3, 34.6, 33.58, 33.56, 30.3, 15.7; IR (neat) 2974, 2917, 1746, 1213, 1051 cm^{-1}; HRMS (EI) *m*/*z* 168 (M)$^+$ calcd for $C_{10}H_{16}O_2$ 1168.1150, found 168.1146.

4.2.14. Methyl (4R,5R*)-4-(3-butenyl)-tetrahydro-5-methyl-2-pyrone-3-carboxylate (**13**).* A solution of **15** (263.1 mg, 1.56 mmol) in THF (3 mL) was added dropwise to a solution of LDA, prepared from diisopropylamine (0.50 mL, 3.6 mmol) and *n*-butyllithium (1.65 M in hexane, 2.0 mL, 3.3 mmol) in THF (8 mL), at −78 °C. After 1 h, methyl chloroformate (0.12 mL, 1.6 mmol) was added dropwise. After 1 h, the mixture was treated with 10% aqueous NH_4Cl solution, and extracted with hexane/EtOAc (3:1 v/v, three times). The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 4:1 v/v) to afford **13** (337.7 mg, 96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, ddt, *J* 17.2, 10.4, 6.4 Hz), 5.03 (1H, ddt, *J* 17.2, 1.6, 1.6 Hz), 5.00 (1H, ddt, *J* 10.4, 1.6, 1.6 Hz), 4.22 (1H, dd, *J* 11.2, 4.0 Hz), 3.99 (1H, dd, *J* 11.2, 8.4 Hz), 3.80 (3H, s), 3.36 (1H, d, *J* 8.0 Hz), 2.15–2.04 (3H, m), 1.89–1.78 (1H, m), 1.60–1.45 (2H, m), 1.06 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.5, 137.4, 115.7, 72.6, 53.1, 52.5, 40.8, 33.3, 33.0, 30.0, 16.6; IR (neat) 2958, 2929, 1732, 1157 cm^{-1}; HRMS (EI) *m*/*z* 226 (M)$^+$ calcd for $C_{12}H_{18}NO_4$ 226.1205, found 226.1214.

*4.2.15. Typical procedure of second generation palladium-catalyzed cycloalkenylation of **13**.* (Table 2, entry 6) To a solution of **13** (100.8 mg, 0.445 mmol) in DMSO (3 mL) were added $Pd(OAc)_2$ (5.0 mg, 0.022 mmol) and LiCl (7.7 mg, 0.089 mmol). The mixture was stirred at 45 °C under 1 atm of oxygen. After 12 h, the mixture was treated with aqueous NaCl solution, extracted with hexane/EtOAc (1:1 v/v, three times). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 3:1 v/v) to provide a mixture of **12** and **17** (92.6 mg, 93%) as a colorless oil. Each compound was isolated by HPLC (hexane/EtOAc 3:1 v/v).

4.2.16. Methyl (1S,5R*,6R*)-5-methyl-9-methylene-2-oxo-3-oxabicyclo-[4.3.0]nonane-1-carboxylate (**12**-exo).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (1H, dd, *J* 2.4, 2.4 Hz), 5.31 (1H, dd, *J* 2.0, 2.0 Hz), 4.20 (1H, dd, *J* 11.2, 4.0 Hz), 3.89 (1H, dd, *J* 11.2, 11.2 Hz), 3.78 (3H, s), 2.62 (1H, ddd, *J* 9.2, 6.4, 6.4 Hz), 2.54–2.41 (2H, m), 1.98 (1H, ddq, *J* 8.8, 6.8, 6.8 Hz), 1.84–1.72 (1H, m), 1.57 (1H, dddd, *J* 13.2, 7.6, 7.6, 6.0 Hz), 1.04 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 168.6, 146.7, 113.5, 73.2, 63.0, 53.5, 50.5, 32.3, 31.1, 28.8, 15.4; IR (neat) 2957, 1732, 1236 cm^{-1}; HRMS (EI) *m*/*z* 224 (M)$^+$ calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1048.

4.2.17. Methyl (1S,5R*,6R*)-5,9-dimethyl-2-oxo-3-oxabicyclo[4.3.0] nona-8-ene-1-carboxylate (**12**-endo).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70–5.60 (1H, m), 4.19 (1H, dd, *J* 11.2, 3.6 Hz), 3.95 (1H, dd, *J* 11.2, 9.6 Hz), 3.78 (3H, s), 2.74 (1H, dddd, *J* 16.4, 8.8, 2.4, 2.4 Hz), 2.66 (1H, ddd, *J* 8.8, 8.8, 4.0 Hz), 2.11 (1H, dddq, *J* 16.4, 4.0, 2.4, 2.4 Hz), 1.89–1.77 (4H, m), 1.05 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 168.9, 137.3, 130.5, 72.4, 70.0, 53.3, 49.2, 37.4, 35.4, 15.8, 15.1; IR (neat) 2957, 1730, 1244 cm^{-1}; HRMS (EI) *m*/*z* 224 (M)$^+$ calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1049.

4.2.18. Methyl (1R,5R*,6R*,9R*)-5,9-dimethyl-2-oxo-3-oxabicyclo [4.3.0]nona-7-ene-1-carboxylate (**17a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (1H, ddd, *J* 6.0, 2.4, 1.6 Hz), 5.63 (1H, ddd, *J* 6.0, 2.4, 1.6 Hz), 4.26 (1H, dd, *J* 10.8, 3.6 Hz), 4.07 (1H, dd, *J* 10.8, 9.6 Hz), 3.76–3.72 (4H, m), 2.81 (1H, ddd, *J* 9.6, 2.4, 1.6 Hz), 1.84–1.72 (1H, m),

1.08–1.04 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 169.5, 137.5, 127.8, 73.7, 61.4, 56.0, 53.4, 46.4, 35.0, 18.2, 15.0; IR (neat) 1747, 1729, 1235 cm^{-1}; HRMS (EI) *m*/*z* 224 (M)$^+$ calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1037.

4.2.19. Methyl (1R,5R*,6R*,9S*)-5,9-dimethyl-2-oxo-3-oxabicyclo [4.3.0]nona-7-ene-1-carboxylate (**17b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63–5.57 (2H, m), 4.07 (1H, dd, *J* 10.8, 4.0 Hz), 3.84–3.78 (2H, m), 3.78 (3H, s), 3.51 (1H, dddd, *J* 10.0, 2.0, 2.0, 2.0 Hz), 1.80–1.68 (1H, m), 1.10 (3H, d, *J* 6.8 Hz), 1.02 (3H, d, *J* 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.2, 134.9, 128.8, 71.7, 62.4, 54.4, 53.2, 47.3, 45.0, 16.2, 16.1; IR (neat) 2964, 1732, 1242, 1191, 1161 cm^{-1}; HRMS (EI) *m*/*z* 224 (M)$^+$ calcd for $C_{12}H_{16}O_4$ 224.1049, found 224.1039.

*4.2.20. (±)-Isodihydronepetalactone (**11**)[9].* A solution of **12** (89.1 mg, 0.397 mmol) in MeOH (3 mL) in the presence of 10% Pd/C (20 mg) was stirred under 1 atm of hydrogen. After 42 h, the reaction mixture was filtered through Celite® and concentrated under reduced pressure. The residual oil was dissolved in DMSO (2.0 mL) and H_2O (0.4 mL). LiCl (181 mg, 4.27 mmol) was added, and the resulting mixture was heated at 160 °C for 8 h. After the mixture was cooled to rt, aqueous NaCl solution was added, and extracted with hexane/EtOAc (3:1 v/v, three times). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 3:1 v/v) to afford **11** with its diastereomer (9:1) (57.2 mg, 86% for two steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (1H, dd, *J* 10.8, 3.2 Hz), 3.87 (1H, dd, *J* 10.8, 10.8 Hz), 2.34 (1H, dd, *J* 10.8, 8.8 Hz), 2.28 (1H, ddd, *J* 10.0, 6.4, 6.4 Hz), 2.13–1.98 (2H, m), 1.86 (1H, dddd, *J* 12.0, 6.0, 6.0, 2.0 Hz), 1.60 (1H, ddqd, *J* 9.6, 9.6, 6.8, 3.2 Hz), 1.23–1.10 (2H, m), 1.20 (3H, d, *J* 6.8 Hz), 0.99 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 73.0, 49.1, 44.8, 38.9, 35.3, 34.5, 32.0, 20.4, 15.9; IR (neat) 2956, 1733, 1182, 1051 cm^{-1}; HRMS (EI) *m*/*z* 168 (M)$^+$ calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1161.

The ^{1}H NMR data was in complete agreement with the reported values.[9]

4.2.21. (R)-2-[(1R*,2R*,3S*)-2-(Hydroxymethyl)-3-methylcyclopentyl]propan-1-ol (**16**)[10].* A solution of **11** (65.9 mg, 0.392 mmol) in THF (4 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (44.3 mg, 1.17 mmol) in THF (4 mL) at 0 °C. After 1 h, saturated aqueous Na_2SO_4 solution (0.8 mL) was added dropwise, and then the mixture was allowed to warm to rt. The resulting white solid was filtered off and the filtrate was concentrated. The residue was subjected to flash chromatography (EtOAc) to afford **16** (64.4 mg, 95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (1H, dd, *J* 10.4, 7.2 Hz), 3.54 (1H, dd, *J* 10.4, 6.0 Hz), 3.49 (1H, dd, *J* 10.4, 5.6 Hz), 3.40 (1H, dd, *J* 10.4, 5.6 Hz), 2.69 (2H, br s), 1.88–1.72 (6H, m), 1.34–1.20 (1H, m), 1.10–0.97 (1H, m), 1.01 (3H, d, *J* 6.8 Hz), 0.90 (3H, d, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.1, 63.6, 50.6, 44.9, 37.2, 35.5, 32.1, 29.3, 22.6, 16.9; IR (neat) 3262, 2949, 2866, 1455, 1016, 830 cm^{-1}.

*4.2.22. (±)-Isoiridomyrmecin (**10**)[9,12].* Pyridine (5.8 mL, 73 μmol), MS 3 Å (180 mg), and $Pd(OAc)_2$ (4.1 mg, 18 μmol) were added to a solution of **16** (62.7 mg, 0.364 mmol) in toluene (4 mL). The mixture was heated at 60 °C under 1 atm of oxygen. After 12 h, the mixture was filtered through Celite®, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 3:1 v/v) to provide mixture of **10** and **11** (54.9 mg, 90%, **10**:**11**=1:1) as a colorless oil. Compound **10** was isolated by HPLC (hexane/2-propanol 20:1 v/v): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38–4.33 (1H, m), 3.99–3.92 (1H, m), 2.31 (1H, dq, *J* 10.0, 6.4 Hz), 2.17–1.97 (3H, m), 1.95–1.84 (2H, m), 1.65 (1H, ddq, *J* 10.0, 6.8, 6.8 Hz), 1.37–1.21 (5H, m), 1.19 (3H, d, *J* 6.4 Hz), 1.05 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 69.6, 45.4, 43.3, 39.2, 38.4, 35.4, 33.2, 19.3, 14.1 cm^{-1}; HRMS (EI) *m*/*z* 168 (M)$^+$ calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1151.

The ^{1}H NMR data was in complete agreement with the reported values.[9,12]

*4.2.23. 4-(3-Butenyl)-1-methylpyrrolidin-2-one (**23**).* A mixture of **22** (1.00 g, 7.13 mmol), TsOH (1.94 g, 10.2 mmol), and 40% aqueous methylamine solution (2.5 mL, 29 mmol) in dioxane (5 mL) was heated in a stainless autoclave at 220 °C. After 14 h, the reaction mixture was allowed to cool to rt, and then poured into saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc (three times). The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (EtOAc/MeOH 20:1 v/v) to provide **23** (755.0 mg, 69%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* 16.8, 10.0, 6.8 Hz), 5.06–4.96 (2H, m), 3.46 (1H, dd, *J* 9.6, 8.0 Hz), 3.02 (1H, dd, *J* 9.6, 6.8 Hz), 2.83 (3H, s), 2.51 (1H, dd, *J* 16.4, 8.8 Hz), 2.42–2.29 (1H, m), 2.11–2.02 (3H, m), 1.55 (2H, dt, *J* 7.6, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 137.8, 115.4, 55.4, 37.5, 34.1, 31.8, 31.1, 29.7; IR (neat) 2925, 1676, 1502, 1404 cm^{-1}; HRMS (EI) *m*/*z* 153 (M)$^+$ calcd for $C_9H_{15}NO$ 153.1154, found 153.1152.

*4.2.24. Methyl 4-(3-butenyl)-1-methyl-2-oxopyrrolidine-3-carboxylate (**18a**).* A solution of **23** (462.0 mg, 3.01 mmol) in THF (5 mL) was added dropwise to a solution of LDA, prepared from diisopropylamine (1.5 mL, 11 mmol) and *n*-butyllithium (1.66 M in hexane, 5.0 mL, 8.3 mmol) in THF (10 mL), at −78 °C. After 1 h, methyl chloroformate (0.28 mL, 3.5 mmol) was added dropwise. After 1 h, the mixture was treated with 10% aqueous NH_4Cl solution and extracted with EtOAc (three times). The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 1:2 v/v) to afford **18a** (546.1 mg, 86%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J* 17.2, 10.0, 6.8 Hz), 5.06–4.97 (2H, m), 3.73 (0.3H, s), 3.70 (2.7H, s), 3.55 (0.9H, dd, *J* 9.6, 8.4 Hz), 3.39 (0.1H, dd, *J* 19.6, 8.8 Hz), 3.30 (0.1H, dd, *J* 9.6, 9.6 Hz), 3.14 (0.9H, d, *J* 8.0 Hz), 3.01 (0.9H, dd, *J* 9.2, 6.8 Hz), 2.90 (0.3H, s), 2.86 (2.7H, s), 2.81–2.71 (1H, m), 2.12–2.02 (2H, m), 1.70–1.51 (2H, m); IR (neat) 2928, 1739, 1695, 1435, 1268 cm^{-1}; HRMS (EI) *m*/*z* 211 (M)$^+$ calcd for $C_{11}H_{17}NO_3$ 211.1208, found 211.1201.

*4.2.25. Methyl 1-benzyl-4-(3-butenyl)-2-oxopyrrolidine-3-carboxylate (**18b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.22 (5H, m), 5.72 (1H, ddt, *J* 17.2, 10.4, 6.8 Hz), 5.02–4.92 (2H, m), 4.63 (0.1H, d, *J* 15.2 Hz), 4.47 (0.9H, d, *J* 14.8 Hz), 4.45 (0.9H, d, *J* 14.5 Hz), 4.39 (0.1H, d, *J* 15.2 Hz), 3.80 (0.3H, s), 3.81 (2.7H, s), 3.49 (0.1H, d, *J* 8.8 Hz), 3.43 (0.9H, dd, *J* 9.6, 8.0 Hz), 3.25 (0.1H, dd, *J* 8.0, 8.0 Hz), 3.21 (0.9H, d, *J* 8.4 Hz), 3.15 (0.1H, dd, *J* 19.2, 9.6 Hz), 2.87 (0.9H, dd, *J* 9.6, 7.2 Hz), 2.79–2.68 (1H, m), 2.06–1.94 (2H, m), 1.66–1.38 (2H, m); IR (neat) 1740, 1694, 1434, 1268, 1167 cm^{-1}; HRMS (EI) *m*/*z* 287 (M)$^+$ calcd for $C_{17}H_{21}NO_3$ 287.1521, found 287.1519.

*4.2.26. Methyl 4-(3-butenyl)-1-tert-butyl-2-oxopyrrolidine-3-carboxylate (**18c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, ddt, *J* 17.2, 10.4, 6.8 Hz), 5.06–4.96 (2H, m), 3.78 (0.9H, s), 3.72 (0.3H, s), 3.64 (0.9H, dd, *J* 9.6, 8.4 Hz), 3.50 (0.1H, dd, *J* 8.8, 7.6 Hz), 3.34 (0.1H, d, *J* 8.8 Hz), 3.28 (0.1H, dd, *J* 9.6, 9.6 Hz), 3.11 (0.9H, d, *J* 9.2 Hz), 2.71–2.61 (1H, m), 2.10–2.02 (2H, m), 1.65–1.44 (2H, m), 1.40 (0.9H, s), 1.39 (8.1H, s); IR (neat) 1741, 1689, 1253, 1228, 1164 cm^{-1}; HRMS (EI) *m*/*z* 253 (M)$^+$ calcd for $C_{14}H_{23}NO_3$ 253.1678, found 253.1688.

*4.2.27. Benzyl 4-(3-butenyl)-1-tert-butyl-2-oxopyrrolidine-3-carboxylate (**18d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.25 (5H, m), 5.73

(1H, ddt, *J* 17.2, 10.4, 6.8 Hz), 5.23 (0.9H, d, *J* 12.4 Hz), 5.19 (0.9H, d, *J* 12.4 Hz), 5.19 (0.1H, d, *J* 12.0 Hz), 5.11 (0.1H, d, *J* 12.0 Hz), 5.01–4.93 (2H, m), 3.64 (0.8H, dd, *J* 9.2, 8.0 Hz), 3.48 (0.2H, dd, *J* 8.8, 7.6 Hz), 3.37 (0.2H, d, *J* 8.8 Hz), 3.24 (0.2H, dd, *J* 9.6, 9.6 Hz), 3.15 (0.8H, d, *J* 8.4 Hz), 3.01 (0.8H, dd, *J* 9.6, 7.2 Hz), 2.69–2.59 (1H, m), 2.05–1.98 (2H, m), 1.62–1.46 (2H, m), 1.38 (7.2H, s), 1.37 (1.8H, s); IR (neat) 1738, 1687, 1154 cm^{-1}; HRMS (EI) *m*/*z* 329 $(M)^+$ calcd for $C_{20}H_{27}NO_3$ 329.1991, found 329.1991.

*4.2.28. Isopropyl 4-(3-butenyl)-1-tert-butyl-2-oxopyrrolidine-3-carboxylate (**18e**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (1H, ddt, *J* 17.2, 10.4, 6.8 Hz), 5.11–4.96 (3H, m), 3.63 (0.9H, dd, *J* 9.6, 8.0 Hz), 3.49 (0.1H, dd, *J* 8.8, 7.6 Hz), 3.29–3.24 (0.2H, m), 3.04 (0.9H, d, *J* 8.8 Hz), 3.00 (0.8H, dd, *J* 9.6, 7.2 Hz), 2.66–2.56 (1H, m), 2.12–2.02 (2H, m), 1.64–1.49 (2H, m), 1.40 (0.9H, s), 1.38 (8.1H, s), 1.31–1.22 (6H, m); IR (neat) 2979, 1734, 1688, 1107 cm^{-1}; HRMS (EI) *m*/*z* 281 $(M)^+$ calcd for $C_{16}H_{27}NO_3$ 281.1991, found 281.1987.

*4.2.29. 3-(2-Hydroxyethyl)-N-methyl-6-heptenamide (**25**).* A mixture of **24** (401.0 mg, 2.60 mmol) and 40% aqueous methylamine solution (1.0 mL, 12 mmol) in dioxane (5 mL) was heated in a stainless autoclave at 200 °C. After 14 h, the reaction mixture was allowed to cool to rt, and then concentrated. The residue was subjected to flash chromatography (EtOAc/MeOH 20:1 v/v) to provide **25** (302.9 mg, 63%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, br s), 5.78 (1H, ddt, *J* 17.2, 10.4, 6.8 Hz), 5.00 (1H, ddt, *J* 17.2, 2.0, 1.6 Hz), 4.94 (1H, ddt, *J* 10.4, 2.0, 1.2 Hz), 3.65 (2H, dd, *J* 6.8, 5.2 Hz), 3.12 (1H, br s), 2.80 (3H, d, *J* 5.2 Hz), 2.26–1.94 (6H, m), 1.74–1.63 (1H, m), 1.47–1.37 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 138.6, 114.8, 60.3, 41.1, 37.0, 34.5, 31.7, 31.2, 26.5; IR (neat) 3300, 2931, 1641, 1563, 1413 cm^{-1}; HRMS (EI) *m*/*z* 185 $(M)^+$ calcd for $C_{10}H_{19}NO_2$ 185.1416, found 185.1419.

*4.2.30. N-Benzyl-3-(2-hydroxyethyl)-6-heptenamide (**27**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (5H, m), 5.91 (1H, br s), 5.79 (1H, ddt, *J* 17.2, 10.4, 6.8 Hz), 5.00 (1H, ddt, *J* 17.2, 1.6, 1.6 Hz), 4.95 (1H, ddt, *J* 10.4, 2.0, 1.2 Hz), 4.45 (2H, d, *J* 5.6 Hz), 3.67 (2H, dd, *J* 6.4, 5.6 Hz), 2.31 (1H, dd, *J* 14.0, 4.8 Hz), 2.22–2.03 (4H, m), 1.73 (1H, dtd, *J* 14.0, 6.8, 4.8 Hz), 1.51–1.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 138.6, 138.3, 128.9, 128.4, 127.8, 114.9, 60.5, 43.9, 41.2, 37.2, 34.5, 31.7, 31.2; IR (neat) 3287, 2927, 1641, 1550 cm^{-1}; HRMS (EI) *m*/*z* 261 $(M)^+$ calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1730.

*4.2.31. N-Benzyl-5-hydroxypentanamide (**29**)*[20]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (5H, m), 5.79 (1H, br s), 4.45 (2H, d, *J* 5.6 Hz), 3.65 (2H, dt, *J* 6.4, 6.3 Hz), 2.28 (2H, t, *J* 7.2 Hz), 1.78 (2H, t, *J* 7.2 Hz), 1.66–1.57 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 138.4, 128.9, 128.0, 127.7, 62.3, 43.8, 36.2, 32.2, 21.7; IR (neat) 3287, 2927, 1641, 1550 cm^{-1}.

*4.2.32. 2-(2-Hydroxyethyl)-N-methylbenzamide (**31**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (2H, m), 7.29–7.21 (2H, m), 6.58 (1H, br s), 4.27 (1H, br s), 3.89 (2H, t, *J* 5.6 Hz), 2.99–2.92 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 138.5, 136.7, 130.8, 130.7, 127.2, 126.6, 64.0, 36.0, 27.0; IR (neat) 3238, 1630, 1599, 1551 cm^{-1}; HRMS (FAB) *m*/*z* 180 $(M+H)^+$ calcd for $C_{10}H_{14}NO_2$ 180.1025, found 180.1028.

*4.2.33. 4-(3-Butenyl)-1-methylpiperidin-2-one (**26**).* To a stirred mixture of **25** (302.9 mg, 1.63 mmol) and pyridine (0.8 mL, 10 mmol) in CH_2Cl_2 (8 mL) was added dropwise a solution of phosphoryl chloride (0.20 mL, 2.2 mmol) at −78 °C, and then the reaction mixture was allowed to warm to rt. After 2 h, the mixture was treated with 10% aqueous NH_4Cl solution at 0 °C, and extracted with EtOAc (three times). The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (EtOAc) to provide **26** (207.0 mg, 76%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* 16.8, 10.4, 6.8 Hz), 5.02 (1H, ddt, *J* 16.8, 2.0, 1.6 Hz), 4.96 (1H, ddt, *J* 10.4, 2.0, 1.2 Hz), 3.33–3.22 (2H, m), 2.93 (3H, s), 2.51 (1H, ddd, *J* 17.2, 4.8, 2.0 Hz), 2.12–2.05 (2H, m), 2.01–1.75 (3H, m), 1.52–1.35 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 138.2, 115.1, 49.2, 38.6, 34.8, 34.5, 32.5, 30.8, 29.1; IR (neat) 2920, 1624, 1509, 1341 cm^{-1}; HRMS (EI) *m*/*z* 167 $(M)^+$ calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1307.

*4.2.34. 1-Benzyl-4-(3-butenyl)piperidin-2-one (**28**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m), 5.78 (1H, ddt, *J* 17.2, 10.4, 6.8 Hz), 5.02 (1H, ddt, *J* 17.2, 2.0, 1.6 Hz), 4.96 (1H, ddt, *J* 10.4, 2.0, 1.2 Hz), 4.69 (1H, d, *J* 14.8 Hz), 4.50 (1H, d, *J* 14.8 Hz), 3.25–3.14 (2H, m), 2.62 (1H, ddd, *J* 17.2, 5.2, 2.0 Hz), 2.12–2.04 (3H, m), 1.97–1.77 (2H, m), 1.47–1.36 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 138.2, 137.4, 128.7, 128.2, 127.5, 115.1, 50.1, 46.5, 38.8, 34.9, 32.5, 30.8, 29.1; IR (neat) 2919, 1638, 1496, 1452 cm^{-1}; HRMS (EI) *m*/*z* 243 $(M)^+$ calcd for $C_{16}H_{21}NO$ 243.1623, found 243.1615.

*4.2.35. 1-Benzylpiperidin-2-one (**30**)*[21]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m), 4.60 (2H, s), 3.22–3.17 (2H, m), 2.47 (2H, dd, *J* 6.4, 6.4 Hz), 1.84–1.73 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 137.5, 128.7, 128.2, 127.4, 50.2, 47.4, 32.6, 23.3, 21.6; IR (neat) 1624, 1496, 1353 cm^{-1}.

*4.2.36. 3,4-Dihydro-2-methylisoquinolin-1-one (**32**)*[22]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (1H, dd, *J* 7.6, 7.6, 1.6 Hz), 7.35–7.31 (1H, m), 7.18–7.15 (1H, m), 3.57 (2H, dd, *J* 6.8, 6.8 Hz), 3.16 (3H, s), 3.01 (2H, dd, *J* 6.8, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 138.1, 131.6, 129.4, 128.2, 127.1, 127.0, 48.2, 35.3, 28.0; IR (neat) 1646, 1336 cm^{-1}.

*4.2.37. Methyl 4-(3-butenyl)-1-methyl-2-oxopiperidine-3-carboxylate (**19a**).* A solution of **26** (64.4 mg, 0.385 mmol) in THF (3 mL) was added dropwise to a stirred solution of LDA, prepared from diisopropylamine (0.20 mL, 1.4 mmol) and *n*-butyllithium (1.66 M in hexane, 0.60 mL, 1.0 mmol) in THF (3 mL), at −78 °C. After 1 h, methyl chloroformate (0.04 mL, 0.5 mmol) was added dropwise. After 1 h, the mixture was treated with water, and extracted with EtOAc (1:1 v/v, three times). The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (EtOAc) to provide **19a** (77.2 mg, 89%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J* 17.2, 10.4, 6.8 Hz), 5.06–4.96 (2H, m), 3.77 (1.5H, s), 3.72 (1.5H, s), 3.53 (0.5H, d, *J* 4.4 Hz), 3.41–3.25 (2H, m), 3.12 (0.5H, d, *J* 9.6 Hz), 2.98 (1.5H, s), 2.95 (1.5H, s), 2.27–1.97 (4H, m), 1.76–1.69 (0.5H, m), 1.56–1.28 (2.5H, m); IR (neat) 2929, 1739, 1644, 1163 cm^{-1}; HRMS (EI) *m*/*z* 225 $(M)^+$ calcd for $C_{12}H_{19}NO_3$ 225.1365, found 225.1354.

*4.2.38. Methyl 1-benzyl-4-(3-butenyl)-2-oxopiperidine-3-carboxylate (**19b**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (5H, m), 5.81–5.70 (1H, m), 5.06–4.95 (2H, m), 4.89 (0.6H, d, *J* 15.2 Hz), 4.69 (0.4H, d, *J* 14.8 Hz), 4.51 (0.4H, d, *J* 14.8 Hz), 4.37 (0.6H, d, *J* 15.2 Hz), 3.80 (1.2H, s), 3.75 (1.8H, s), 3.63 (0.6H, d, *J* 5.6 Hz), 3.32–3.17 (2.4H, m), 2.29–1.95 (4H, m), 1.71–1.29 (3H, m); IR (neat) 1738, 1644, 1496, 1453, 1163 cm^{-1}; HRMS (EI) *m*/*z* 301 $(M)^+$ calcd for $C_{18}H_{23}NO_3$ 301.1678, found 301.1678.

*4.2.39. Methyl 4-(3-butenyl)-1-tert-butyl-2-oxopiperidine-3-carboxylate (**19c**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.82–5.71 (1H, m), 5.05–4.94 (2H, m), 3.76 (1.5H, s), 3.70 (1.5H, s), 3.54–3.48 (1H, m), 3.42 (0.5H, ddd, *J* 12.4, 5.2, 5.2 Hz), 3.31–3.16 (1H, m), 3.10 (0.5H, d, *J* 9.6 Hz), 2.18–1.88 (4H, m), 1.75–1.69 (0.5H, m), 1.52–1.24 (11.5H,

m); IR (neat) 2926, 1739, 1643, 1326, 1201, 1153 cm^{-1}; HRMS (EI) *m/z* 267 $(M)^+$ calcd for $C_{15}H_{25}NO_3$ 267.1834, found 267.1831.

*4.2.40. Benzyl 4-(3-butenyl)-1-methyl-2-oxopiperidine-3-carboxylate (**19d**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (5H, m), 5.73–5.62 (1H, m), 5.27–5.10 (2H, m), 4.99–4.90 (2H, m), 3.57 (0.5H, d, *J* 4.0 Hz), 3.41–3.24 (2H, m), 3.15 (0.5H, d, *J* 9.6 Hz), 2.98 (1.5H, s), 2.96 (1.5H, s), 2.27–1.92 (4H, m), 1.72–1.66 (0.5H, m), 1.64–1.23 (2.5H, m); IR (neat) 1734, 1645, 1156 cm^{-1}; HRMS (EI) *m/z* 301 $(M)^+$ calcd for $C_{18}H_{23}NO_3$ 301.1678, found 301.1678.

*4.2.41. Isopropyl 4-(3-butenyl)-1-methyl-2-oxopiperidine-3-carboxylate (**19e**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.82–5.70 (1H, m), 5.14–4.95 (3H, m), 3.47 (0.5H, dd, *J* 5.6, 1.2 Hz), 3.41–3.24 (2H, m), 3.05 (0.5H, d, *J* 10.0 Hz), 2.97 (1.5H, s), 2.94 (1.5H, s), 2.26 (4H, m), 1.72–1.22 (9H, m); IR (neat) 1731, 1645, 1107 cm^{-1}; HRMS (EI) *m/z* 253 $(M)^+$ calcd for $C_{14}H_{23}NO_3$ 253.1678, found 253.1677.

4.2.42. Methyl (1R,5S*)-3-methyl-8-methylene-2-oxo-3-azabicyclo[3.3.0]octane-1-carboxylate (**33a**).* To a solution of lactam ester **18a** (105.6 mg, 0.500 mmol) in toluene (5 mL) were added DMSO (195.5 mg, 2.50 mmol) and $Pd(OAc)_2$ (11.2 mg, 50 μmol). The mixture was stirred at 45 °C under 1 atm of oxygen. After 94 h, the reaction mixture was allowed to cool to rt, filtered through Celite®, and concentrated. The residue was purified by flash silica gel column chromatography (hexane/EtOAc 1:3 v/v) to provide mixture of **33a** and **34a** (79.7 mg, 76%, 2.6:1) as a colorless oil. Each compound was isolated by HPLC (hexane/EtOAc 1:3 v/v): ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (1H, dd, *J* 2.0, 2.0 Hz), 5.24 (1H, dd, *J* 2.0, 2.0 Hz), 3.75 (3H, s), 3.61 (1H, dd, *J* 10.0, 7.6 Hz), 3.16 (1H, dddd, *J* 7.6, 7.6, 7.6, 2.8 Hz), 3.02 (1H, dd, *J* 10.0, 2.8 Hz), 2.87 (3H, s), 2.49–2.43 (2H, m), 2.11 (1H, dddd, *J* 12.8, 7.2, 7.2, 5.2 Hz), 1.49 (1H, dddd, *J* 12.8, 8.8, 8.8, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.1, 146.9, 111.8, 64.7, 53.0, 52.5, 43.0, 34.0, 31.4, 30.6; IR (neat) 2953, 1742, 1694, 1434, 1240 cm^{-1}; HRMS (EI) *m/z* 209 $(M)^+$ calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1053.

4.2.43. Methyl (1R,5S*)-3,8-dimethyl-2-oxo-3-azabicyclo[3.3.0]octa-7-ene-1-carboxylate (**34a**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.56–5.53 (1H, m), 3.75(3H, s), 3.66 (1H, dd, *J* 9.2, 9.2 Hz), 3.21 (1H, dddd, *J* 9.2, 8.0, 5.2, 2.0 Hz), 2.97 (1H, dd, *J* 9.6, 5.2 Hz) 2.84 (3H, s), 2.70 (1H, dddq, *J* 16.8, 8.0, 2.0, 2.0 Hz), 2.14 (1H, dddq, *J* 16.8, 2.0, 2.0, 2.0 Hz), 1.93 (3H, ddd, *J* 2.0, 2.0, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.1, 137.2, 128.4, 70.3, 55.2, 52.7, 41.1, 38.1, 30.1, 14.0; IR (neat) 2953, 2924, 1739, 1693, 1434, 1255 cm^{-1}; HRMS (EI) *m/z* 209 $(M)^+$ calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1056.

4.2.44. Methyl (1R,5S*)-3-benzyl-8-methylene-2-oxo-3-azabicyclo[3.3.0]octane-1-carboxylate (**33b**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (5H, m), 5.64 (1H, dd, *J* 2.0, 2.0 Hz), 5.29 (1H, dd, *J* 2.0, 2.0 Hz), 4.50 (1H, d, *J* 14.8 Hz), 4.44 (1H, d, *J* 14.8 Hz), 3.75 (3H, s), 3.47 (1H, dd, *J* 10.0, 7.6 Hz), 3.09 (1H, dddd, *J* 7.6, 7.6, 7.6, 2.4 Hz), 2.90 (1H, dd, *J* 10.0, 2.4 Hz), 2.50–2.42 (2H, m), 2.04 (1H, dddd, *J* 12.4, 7.2, 7.2, 4.8 Hz), 1.39 (1H, dddd, *J* 12.4, 9.6, 8.0, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.3, 146.8, 136.2, 128.8, 128.2, 127.8, 112.1, 65.0, 53.1, 49.5, 47.5, 43.1, 34.1, 31.4; IR (neat) 1744, 1692, 1432, 1258, 1242 cm^{-1}; HRMS (EI) *m/z* 285 $(M)^+$ calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1366.

4.2.45. Methyl (1R,5S*)-3-benzyl-8-methyl-2-oxo-3-azabicyclo[3.3.0]octa-7-ene-1-carboxylate (**34b**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.19 (5H, m), 5.57–5.54 (1H, m), 4.46 (2H, s), 3.78 (3H, s), 3.52 (1H, dd, *J* 10.0, 9.2 Hz), 3.18 (1H, dddd, *J* 8.4, 8.0, 5.2, 2.4 Hz), 2.85 (1H, dd, *J* 10.0, 5.2 Hz), 2.67 (1H, dddq, *J* 16.4, 8.0, 2.4, 2.4 Hz), 2.07 (1H, dddq, *J* 16.4, 2.4, 2.0, 2.0 Hz), 1.99 (3H, ddd, *J* 2.0, 2.0, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.3, 137.2, 136.3, 128.8, 128.6, 128.0, 127.7, 70.4, 52.8, 52.2, 46.9, 41.3, 38.1, 14.0; IR (neat) 1738, 1687, 1432, 1256 cm^{-1}; HRMS (EI) *m/z* 285 $(M)^+$ calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1362.

4.2.46. Methyl (1R,5S*)-3-tert-butyl-8-methylene-2-oxo-3-azabicyclo[3.3.0]octane-1-carboxylate (**33c**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (1H, dd, *J* 2.0, 2.0 Hz), 5.23 (1H, dd, *J* 2.0, 2.0 Hz), 3.73 (3H, s), 3.64 (1H, dd, *J* 10.0, 7.2 Hz), 3.15 (1H, dd, *J* 10.0, 2.0 Hz), 3.00 (1H, dddd, *J* 8.8, 7.2, 7.2, 2.0 Hz), 2.47–2.42 (2H, m), 2.60 (1H, dddd, *J* 11.2, 7.2, 7.2, 5.2 Hz), 1.45 (1H, dddd, *J* 12.8, 8.8, 8.8, 8.8 Hz), 1.38 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.2, 147.0, 111.7, 66.3, 54.5, 52.9, 48.4, 42.4, 34.0, 31.1, 27.5; IR (neat) 2957, 1745, 1691, 1404, 1237, 1154 cm^{-1}; HRMS (EI) *m/z* 251 $(M)^+$ calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1522.

4.2.47. Methyl (1R,5S*)-3-tert-butyl-8-methyl-2-oxo-3-azabicyclo[3.3.0]octa-7-ene-1-carboxylate (**34c**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.55–5.52 (1H, m), 3.75(3H, s), 3.72 (1H, dd, *J* 9.6, 8.4 Hz), 3.09 (1H, dddd, *J* 8.0, 8.0, 5.6, 2.4 Hz), 2.99 (1H, dd, *J* 9.6, 5.6 Hz), 2.64 (1H, dddq, *J* 16.8, 7.6, 2.0, 2.0 Hz), 2.09 (1H, dddq, *J* 16.8, 2.0, 2.0, 2.0 Hz), 1.92 (3H, ddd, *J* 2.0, 2.0, 2.0 Hz), 1.38 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.3, 137.6, 128.1, 71.3, 54.5, 52.6, 51.0, 40.5, 37.7, 27.6, 14.1; IR (neat) 2960, 2925, 1737, 1672, 1255, 1056 cm^{-1}; HRMS (EI) *m/z* 251 $(M)^+$ calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1522.

4.2.48. Methyl (1S,5S*)-3-tert-butyl-8-methyl-2-oxo-3-azabicyclo[3.3.0]octa-6-ene-1-carboxylate (**35**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (1H, ddd, *J* 6.0, 2.0, 2.0 Hz), 5.46 (1H, ddd, *J* 6.0, 2.4, 2.4 Hz), 3.74 (3H, s), 3.65 (1H, dd, *J* 9.2, 8.4 Hz), 3.62–3.48 (2H, m), 3.20 (1H, dd, *J* 9.2, 2.0 Hz), 1.37 (9H, s), 1.23 (3H, d, *J* 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.0, 137.7, 128.7, 64.9, 54.5, 52.8, 49.1, 47.8, 45.8, 27.4, 16.8; IR (neat) 1741, 1682, 1225 cm^{-1}; HRMS (EI) *m/z* 251 $(M)^+$ calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1522.

4.2.49. Benzyl (1R,5S*)-3-tert-butyl-8-methylene-2-oxo-3-azabicyclo[3.3.0]octane-1-carboxylate (**33d**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (5H, m), 5.54 (1H, dd, *J* 2.0, 2.0 Hz), 5.25 (1H, dd, *J* 2.0, 2.0 Hz), 5.18 (1H, d, *J* 12.8 Hz), 5.16 (1H, d, *J* 12.8 Hz), 3.59 (1H, dd, *J* 10.0, 7.2 Hz), 3.14 (1H, dd, *J* 10.0, 2.0 Hz), 2.95 (1H, dddd, *J* 8.8, 7.2, 7.2, 2.0 Hz), 2.47–2.41 (2H, m), 2.09–2.01 (1H, m), 1.45 (1H, dddd, *J* 12.4, 9.2, 9.2, 9.2 Hz), 1.35 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.1, 146.7, 135.9, 128.6, 128.3, 128.0, 111.9, 67.2, 66.3, 54.5, 48.5, 42.5, 34.1, 31.3, 27.5; IR (neat) 2960, 1743, 1690, 1404, 1252, 1225, 1152 cm^{-1}; HRMS (EI) *m/z* 327 $(M)^+$ calcd for $C_{20}H_{25}NO_3$ 327.1834, found 327.1835.

4.2.50. Benzyl (1R,5S*)-3-tert-butyl-8-methyl-2-oxo-3-azabicyclo[3.3.0]octa-7-ene-1-carboxylate (**34d**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (5H, m), 5.55–5.52 (1H, m), 5.20 (1H, d, *J* 12.8 Hz), 5.18 (1H, d, *J* 12.8 Hz), 3.69 (1H, dd, *J* 9.2, 8.0 Hz), 3.06 (1H, dddd, *J* 8.0, 8.0, 5.2, 2.8 Hz), 3.00 (1H, dd, *J* 9.2, 5.2 Hz), 2.64 (1H, dddq, *J* 16.4, 7.6, 2.4, 2.4 Hz), 2.08 (1H, dddq, *J* 16.4, 2.4, 2.4, 2.4 Hz), 1.94 (3H, ddd, *J* 2.0, 2.0, 2.0 Hz), 1.37 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.3, 137.5, 136.0, 128.6, 128.19, 128.17, 127.9, 71.3, 66.9, 54.5, 51.0, 40.6, 37.9, 27.6, 14.1; IR (neat) 2974, 1739, 1682, 1282, 1256, 1220 cm^{-1}; HRMS (EI) *m/z* 327 $(M)^+$ calcd for $C_{20}H_{25}NO_3$ 327.1834, found 327.1833.

4.2.51. Isopropyl (1R,5S*)-3-tert-butyl-8-methylene-2-oxo-3-azabicyclo[3.3.0]octane-1-carboxylate (**33e**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (1H, dd, *J* 2.0, 2.0 Hz), 5.24 (1H, dd, *J* 2.0, 2.0 Hz), 5.02 (1H, qq, *J* 6.0, 6.0 Hz), 3.64 (1H, dd, *J* 9.6, 6.8 Hz), 3.17 (1H, dd, *J* 10.0, 1.6 Hz), 2.90 (1H, dddd, *J* 9.2, 7.2, 7.2, 1.6 Hz), 2.47–2.40 (2H, m), 2.10–2.01 (1H, m), 1.45–1.36 (1H, m), 1.39 (9H, s), 1.23 (6H, d, *J* 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.1, 146.8, 111.7, 68.9, 66.4, 54.4, 48.5, 42.6, 34.2, 31.5, 27.5, 21.8, 21.7; IR (neat) 2978, 1741, 1691, 1403,

1252, 1231, 1108 cm^{-1}; HRMS (EI) *m/z* 279 $(M)^+$ calcd for $C_{16}H_{25}NO_3$ 279.1834, found 279.1837.

4.2.52. Isopropyl (1R,5S*)-3-tert-butyl-8-methyl-2-oxo-3-aza-bicyclo[3.3.0]octa-7-ene-1-carboxylate (**34e**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.52–5.49 (1H, m), 5.04 (1H, qq, *J* 6.4, 6.4 Hz), 3.73–3.67 (1H, m), 3.06–2.99 (2H, m), 2.65 (1H, dddq, *J* 16.4, 8.0, 2.4, 2.4 Hz), 2.09 (1H, dddq, *J* 16.4, 2.4, 2.4, 2.4 Hz), 1.94 (3H, ddd, *J* 2.4, 2.4, 1.6 Hz), 1.38 (9H, s), 1.25 (3H, d, *J* 6.4 Hz), 1.24 (3H, d, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.7, 137.9, 127.9, 71.2, 67.7, 54.4, 50.9, 40.7, 38.1, 27.6, 21.9, 21.8, 14.1; IR (neat) 2978, 1737, 1684, 1281, 1260, 1235, 1109 cm^{-1}; HRMS (EI) *m/z* 279 $(M)^+$ calcd for $C_{16}H_{25}NO_3$ 279.1834, found 279.1834.

4.2.53. Methyl (1R,6R*)-3-methyl-9-methylene-2-oxo-3-azabicyclo[4.3.0]nonane-1-carboxylate (**36a**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (1H, dd, *J* 2.0, 2.0 Hz), 5.22 (1H, dd, *J* 2.0, 2.0 Hz), 3.73 (3H, s), 3.40 (1H, ddd, *J* 12.0, 9.6, 2.4 Hz), 3.29 (1H, ddd, *J* 12.0, 5.2, 5.2 Hz), 2.98 (3H, s), 2.72 (1H, dddd, *J* 10.4, 6.4, 4.0, 4.0 Hz), 2.62–2.52 (1H, m), 2.51–2.41 (1H, m), 1.89–1.75 (2H, m), 1.66 (1H, dddd, *J* 13.6, 10.0, 10.0, 4.8 Hz), 1.57 (1H, dddd, *J* 12.8, 8.8, 5.2, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.1, 147.8, 112.6, 64.4, 53.0, 48.3, 44.1, 35.5, 30.1, 28.3, 25.3; IR (neat) 2950, 1739, 1643, 1253, 1194 cm^{-1}; HRMS (EI) *m/z* 223 $(M)^+$ calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1205.

4.2.54. Methyl (1R,6R*)-3,9-dimethyl-2-oxo-3-azabicyclo[4.3.0]nona-8-ene-1-carboxylate (**37a**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.63–5.60 (1H, m), 3.73(3H, s), 3.41 (1H, ddd, *J* 12.8, 8.8, 3.6 Hz), 3.29 (1H, ddd, *J* 12.8, 6.4, 4.0 Hz), 2.97 (3H, s) 2.86 (1H, dddd, *J* 8.4, 6.0, 5.2, 5.2 Hz), 2.55–2.46 (1H, m), 2.16–2.02 (2H, m), 1.90 (3H, ddd, *J* 2.0, 2.0, 2.0 Hz), 1.72 (1H, dddd, J 13.6, 6.4, 6.4, 4.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 167.2, 139.5, 129.2, 67.4, 52.7, 46.9, 42.9, 35.9, 35.5, 26.7, 15.4; IR (neat) 2950, 1739, 1642, 1249, 1210 cm^{-1}; HRMS (EI) *m/z* 223 $(M)^+$ calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1202.

4.2.55. Methyl (1R,6R*)-3-benzyl-9-methylene-2-oxo-3-azabicyclo[4.3.0]nonane-1-carboxylate (**36b**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m), 5.60 (1H, dd, *J* 2.4, 2.4 Hz), 5.27 (1H, dd, *J* 2.0, 2.0 Hz), 4.71 (1H, d, *J* 14.8 Hz), 4.54 (1H, d, *J* 14.8 Hz), 3.76 (3H, s), 3.28 (1H, ddd, *J* 12.4, 10.0, 4.0 Hz), 3.20 (1H, ddd, *J* 12.4, 4.8, 4.8 Hz), 2.74 (1H, dddd, *J* 10.4, 6.0, 4.0, 4.0 Hz), 2.58(1H, ddddd, *J* 16.8, 9.6, 5.6, 2.4, 2.4 Hz), 2.49 (1H, ddddd, *J* 16.8, 8.0, 8.0, 2.0, 2.0 Hz), 1.87–1.76 (2H, m), 1.64–1.51 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.2, 147.9, 137.2, 128.7, 128.0, 127.5, 112.7, 64.6, 53.0, 50.5, 45.5, 44.0, 30.2, 28.4, 25.5; IR (neat) 1740, 1638, 1254 cm^{-1}; HRMS (EI) *m/z* 299 $(M)^+$ calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1523.

4.2.56. Methyl (1R,6R*)-3-tert-butyl-9-methyl-2-oxo-3-azabicyclo[4.3.0]nona-8-ene-1-carboxylate (**37b**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.22 (5H, m), 5.67–5.64 (1H, m), 4.68 (1H, d, *J* 15.2 Hz), 4.56 (1H, d, *J* 15.2 Hz), 3.77 (3H, s), 3.28 (1H, ddd, *J* 12.4, 8.8, 4.0 Hz), 3.21 (1H, ddd, *J* 12.4, 6.4, 4.4 Hz), 2.88 (1H, dddd, *J* 8.4, 6.0, 5.2, 5.2 Hz), 2.53 (1H, dddq, *J* 16.4, 8.4, 2.0, 2.0 Hz), 2.10 (1H, dddq, *J* 16.4, 2.4, 2.4, 2.4 Hz), 2.01 (1H, ddd, *J* 13.6, 9.2, 4.4 Hz), 1.95 (3H, ddd, *J* 2.0, 2.0, 2.0 Hz), 1.67 (1H, dddd, *J* 13.6, 6.4, 6.4, 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 167.3, 139.3, 137.2, 129.5, 128.7, 127.9, 127.5, 67.7, 52.7, 50.6, 44.3, 42.9, 36.1, 27.1, 15.4; IR (neat) 1740, 1637, 1247 cm^{-1}; HRMS (EI) *m/z* 299 $(M)^+$ calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1517.

4.2.57. Methyl (1R,6R*)-3-tert-butyl-9-methylene-2-oxo-3-azabicyclo[4.3.0]nonane-1-carboxylate (**36c**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (1H, dd, *J* 2.0, 2.0 Hz), 5.20 (1H, dd, *J* 2.0, 2.0 Hz), 3.72 (3H, s), 3.38 (1H, ddd, *J* 12.4, 6.0, 4.4 Hz), 3.26 (1H, ddd, *J* 12.4, 9.2, 4.0 Hz), 2.72 (1H, dddd, *J* 8.8, 6.8, 5.2, 5.2 Hz), 2.56–2.39 (2H, m), 1.87 (1H, dddd, *J* 14.0, 6.0, 6.0, 4.0 Hz), 1.82 (1H, dddd, *J* 13.2, 9.2, 6.8, 6.8 Hz), 1.61–1.44 (2H, m), 1.41 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 168.1, 148.7, 111.9, 66.3, 57.7, 52.8, 43.1, 42.2, 31.1, 28.9, 28.3, 27.6; IR (neat) 1740, 1639, 1240, 1199 cm^{-1}; HRMS (EI) *m/z* 265 $(M)^+$ calcd for $C_{15}H_{23}NO_3$ 265.1678, found 265.1671.

4.2.58. Methyl (1R,6R*)-3-tert-butyl-9-methyl-2-oxo-3-azabicyclo[4.3.0]nona-8-ene-1-carboxylate (**37c**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.63–5.60 (1H, m), 3.73 (3H, s), 3.34–3.29 (2H, m), 2.88 (1H, dddd, *J* 8.8, 5.6, 5.6, 4.0 Hz), 2.58 (1H, dddq, *J* 16.8, 8.8, 2.4, 2.4 Hz), 2.05–1.94 (2H, m), 1.86 (3H, ddd, *J* 2.4, 2.4, 1.6 Hz), 1.65 (1H, dddd, *J* 13.6, 5.6, 5.6, 3.6 Hz), 1.41 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 168.6, 139.1, 129.6, 70.7, 57.8, 52.4, 41.6, 41.0, 37.1, 30.6, 28.4, 15.2; IR (neat) 1750, 1641, 1245, 1200 cm^{-1}; HRMS (EI) *m/z* 265 $(M)^+$ calcd for $C_{15}H_{23}NO_3$ 265.1678, found 265.1671.

4.2.59. Benzyl (1R,6R*)-3-methyl-9-methylene-2-oxo-3-azabicyclo[4.3.0]nonane-1-carboxylate (**36d**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (5H, m), 5.56 (1H, dd, *J* 2.4, 2.4 Hz), 5.23 (1H, dd, *J* 2.0, 2.0 Hz), 5.22 (1H, d, *J* 12.4 Hz), 5.13 (1H, d, *J* 12.4 Hz), 3.37 (1H, ddd, *J* 12.0, 9.6, 4.4 Hz), 3.27 (1H, ddd, *J* 12.0, 4.8, 4.8 Hz), 2.98 (3H, s), 2.70 (1H, dddd, *J* 10.4, 6.0, 4.4, 4.4 Hz), 2.53 (1H, ddddd, *J* 16.4, 9.6, 5.2, 2.4, 2.4 Hz), 2.46(1H, ddddd, *J* 16.4, 8.0, 8.0, 2.0, 2.0 Hz), 1.81 (1H, dddd, *J* 14.0, 4.8, 4.8, 4.8 Hz), 1.77–1.59 (2H, m), 1.53 (1H, dddd, *J* 12.8, 8.4, 5.2, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 167.0, 147.6, 136.2, 128.6, 128.1, 127.9, 112.7, 67.1, 64.5, 48.3, 44.1, 35.5, 30.2, 28.3, 25.3; IR (neat) 1739, 1641, 1221, 1189 cm^{-1}; HRMS (EI) *m/z* 299 $(M)^+$ calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1523.

4.2.60. Benzyl (1R,6R*)-3,9-dimethyl-2-oxo-3-azabicyclo[4.3.0]nona-8-ene-1-carboxylate (**37d**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (5H, m), 5.62–5.59 (1H, m), 5.27 (1H, d, *J* 12.4 Hz), 5.11 (1H, d, *J* 12.4 Hz), 3.39 (1H, ddd, *J* 12.4, 8.8, 3.6 Hz), 3.27 (1H, ddd, *J* 12.4, 6.4, 4.4 Hz), 2.98 (3H, s), 2.83 (1H, dddd, *J* 8.4, 6.4, 5.2, 5.2 Hz), 2.48 (1H, dddq, *J* 16.4, 8.4, 2.4, 2.4 Hz), 2.10 (1H, dddq, *J* 16.4, 2.4, 2.4, 2.4 Hz), 2.04 (1H, ddd, *J* 13.2, 9.2, 4.4 Hz), 1.92 (3H, ddd, *J* 2.4, 2.4, 1.6 Hz), 1.70 (1H, dddd, *J* 13.2, 6.4, 6.4, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 167.1, 139.4, 136.2, 129.2, 128.6, 128.1, 127.9, 67.4, 66.9, 47.0, 42.9, 35.9, 35.5, 26.8, 15.4; IR (neat) 1737, 1640, 1238, 1208 cm^{-1}; HRMS (EI) *m/z* 299 $(M)^+$ calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1523.

4.2.61. Isopropyl (1R,6R*)-3-methyl-9-methylene-2-oxo-3-azabicyclo[4.3.0]nonane-1-carboxylate (**36e**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.50 (1H, dd, *J* 2.0, 2.0 Hz), 5.19 (1H, dd, *J* 2.0, 2.0 Hz), 5.02 (1H, sept, *J* 6.0 Hz), 3.39 (1H, ddd, *J* 12.4, 10.0, 4.4 Hz), 3.28 (1H, ddd, *J* 12.4, 4.8, 4.8 Hz), 2.97 (3H, s), 2.71 (1H, dddd, *J* 10.4, 6.4, 4.4, 4.4 Hz), 2.54 (1H, ddddd, *J* 16.8, 9.6, 5.6, 2.0, 2.0 Hz), 2.45 (1H, ddddd, *J* 16.8, 8.4, 8.4, 2.0, 2.0 Hz), 1.88–1.74 (2H, m), 1.65 (1H, dddd, *J* 14.0, 10.0, 10.0, 4.8 Hz), 1.54 (1H, dddd, *J* 12.8, 8.4, 5.2, 4.0 Hz), 1.23 (3H, d, *J* 6.0 Hz), 1.20 (3H, d, *J* 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 167.2, 147.8, 112.3, 69.0, 64.6, 48.2, 44.1, 35.4, 30.3, 28.4, 25.4, 21.8, 21.6; IR (neat) 1733, 1644, 1254, 1108 cm^{-1}; HRMS (EI) *m/z* 251 $(M)^+$ calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1510.

4.2.62. Isopropyl (1R,6R*)-3,9-dimethyl-2-oxo-3-azabicyclo[4.3.0]nona-8-ene-1-carboxylate (**37e**).* ^1H NMR (400 MHz, $CDCl_3$) δ 5.59–5.56 (1H, m), 5.03 (1H, sept, *J* 6.4 Hz), 3.39 (1H, ddd, *J* 12.8, 9.2, 4.0 Hz), 3.27 (1H, ddd, *J* 12.8, 6.4, 4.4 Hz), 2.96 (3H, s), 2.83 (1H, dddd, *J* 8.4, 6.0, 5.2, 5.2 Hz), 2.48 (1H, dddq, *J* 16.4, 8.8, 2.0, 2.0 Hz), 2.15–2.02 (2H, m), 1.91 (3H, ddd, *J* 2.4, 2.4, 1.6 Hz), 1.71 (1H, dddd, *J* 12.4, 6.4, 6.4, 4.0 Hz), 1.24 (3H, d, *J* 6.4 Hz), 1.20 (3H, d, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 167.4, 139.7, 128.8, 68.7, 67.4, 46.9, 43.0, 35.8, 35.4, 26.6, 21.8, 21.7, 15.5; IR (neat) 1733, 1644, 1248,

1108 cm^{-1}; HRMS (EI) *m*/*z* 251 $(M)^+$ calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1522.

4.2.63. (S)-3-{(R*)-1-Hydroxypropan-2-yl}-N-methyl-6-heptenamide (**41**).* A mixture of **15** (215.1 mg, 1.278 mmol) and 40% aqueous methylamine solution (2 mL, 23 mmol) in dioxane (8 mL) was heated in a stainless autoclave at 200 °C. After 14 h, the reaction mixture was allowed to cool to rt, and then concentrated. The residue was subjected to flash chromatography (EtOAc/MeOH 20:1 v/v) to provide **41** (260.0 mg, quant.) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (1H, ddt, *J* 16.8, 10.0, 6.8 Hz), 5.60 (1H, br s), 5.00 (1H, ddt, *J* 16.8, 1.6, 1.6 Hz), 4.96 (1H, ddt, *J* 10.0, 1.6, 1.6 Hz), 3.53 (1H, dd, *J* 11.2, 5.2 Hz), 3.51 (1H, dd, *J* 11.2, 6.0 Hz), 2.81 (3H, d, *J* 4.8 Hz), 2.25 (1H, dd, *J* 14.8, 5.2 Hz), 2.17 (1H, dd, *J* 14.8, 8.0 Hz), 2.15–1.95 (4H, m), 1.67 (1H, tdd, *J* 12.0, 6.8, 6.0 Hz), 1.50 (1H, dddd, *J* 14.0, 10.4, 6.0, 4.0 Hz), 1.27 (1H, dddd, *J* 14.0, 9.6, 8.8, 5.6 Hz), 0.91 (3H, d, *J* 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 138.8, 114.8, 65.9, 39.1, 38.6, 35.8, 31.5, 30.0, 26.6, 13.6; IR (neat) 3308, 2931, 1644, 1556, 1384, 1039 cm^{-1}; HRMS (EI) *m*/*z* 199 $(M)^+$ calcd for $C_{11}H_{21}NO_2$ 199.1572, found 199.1572.

4.2.64. (4S,5R*)-4-(3-Butenyl)-1,5-dimethylpiperidin-2-one (**42**).* To a stirred mixture of **41** (105.6 mg, 0.530 mmol) and pyridine (0.21 mL, 2.6 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of phosphoryl chloride (0.06 mL, 0.65 mmol) at −78 °C, and then the reaction mixture was allowed to warm to rt. After 22 h, the mixture was treated with 10% aqueous NH_4Cl solution at 0 °C, and extracted with EtOAc (three times), washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (EtOAc) to provide **42** (70.3 mg, 73%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* 17.2, 10.0, 6.8 Hz), 5.02 (1H, ddt, *J* 17.2, 1.6, 1.6 Hz), 4.97 (1H, ddt, *J* 10.0, 1.6, 1.6 Hz), 3.21 (1H, dd, *J* 12.0, 5.2 Hz), 2.94 (1H, dd, *J* 12.0, 10.0 Hz), 2.92(3H, s), 2.56 (1H, dd, *J* 17.6, 5.2 Hz), 2.19–2.09 (1H, m), 2.01–1.91 (1H, m), 1.99 (1H, dd, *J* 17.6, 10.8 Hz), 1.74–1.62 (2H, m), 1.51 (1H, dddd, *J* 14.8, 5.2, 5.2, 4.0 Hz), 1.18 (1H, dddd, *J* 13.2, 9.6, 9.6, 5.2 Hz), 0.99 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 138.3, 115.1, 56.6, 38.0, 37.0, 34.4, 33.6, 32.1, 30.3, 16.4; IR (neat) 2917, 1651, 1505 cm^{-1}; HRMS (EI) *m*/*z* 181 $(M)^+$ calcd for $C_{11}H_{19}NO$ 181.1467, found 181.1468.

4.2.65. Methyl (4R,5R*)-4-(3-butenyl)-1,5-dimethyl-2-oxopiperidine-3-carboxylate (**40**).* A solution of **42** (270.6 mg, 1.49 mmol) in THF (3 mL)was added dropwise to a stirred solution of LDA, prepared from diisopropylamine (0.45 mL, 3.20 mmol) and *n*-butyllithium (1.66 M in hexane, 1.85 mL, 2.96 mmol) in THF (8 mL), at −78 °C. After 1 h, methyl chloroformate (0.125 mL, 1.61 mmol) was added dropwise. After 1 h, the mixture was treated with water, and extracted with hexane/EtOAc (1:1 v/v, three times). The combined organic layers were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 1:2 v/v) to provide **40** (323.8 mg, 91%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.69 (1H, m), 5.07–4.94 (2H, m), 3.76 (2.28H, s), 3.72 (0.72H, s), 3.62 (0.24H, d, *J* 5.6 Hz), 3.30 (0.24H, dd, *J* 12.0, 5.6 Hz), 3.26 (0.76H, d, *J* 10.8 Hz), 3.17 (0.76H, dd, *J* 12.4, 4.8 Hz), 3.07 (0.76H, dd, *J* 12.4, 10.8 Hz), 3.01 (0.24H, dd, *J* 12.0, 5.6 Hz), 2.96 (0.72H, s), 2.94 (2.28H, s), 2.90 (0.24H, dd, *J* 12.0, 10.8 Hz), 2.11–1.96 (2.76H, m), 1.82 (0.76H, ddqd, *J* 10.8, 10.8, 6.4, 5.2 Hz), 1.74–1.64 (0.48H, m), 1.59–1.41 (1.76H, m), 1.01 (2.28H, d, *J* 6.4 Hz), 0.95 (0.72H, d, *J* 6.4 Hz); IR (neat) 2930, 1740, 1651, 1505, 1453, 1436, 1259, 1159 cm^{-1}; HRMS (EI) *m*/*z* 239 $(M)^+$ calcd for $C_{13}H_{21}NO_3$ 239.1521, found 239.1525.

*4.2.66. Typical procedure of second generation palladium-catalyzed cycloalkenylation of **40**.* (Table 6, entry 5) To a stirred solution of **40** (133.2 mg, 0.556 mmol) in toluene (8 mL) were added DMSO (220 mg, 2.81 mmol) and MS 3 Å (500 mg) followed by $Pd(OAc)_2$ (12.5 mg, 55.6 μmol). The mixture was stirred at 45 °C under 1 atm of oxygen. After 86 h, the reaction mixture was filtered through Celite®, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 1:2 v/v) to provide a mixture of **39** (92.7 mg, 70%) as a colorless oil.

4.2.67. Methyl (1R,5R*,6R*)-3,5-dimethyl-9-methylene-2-oxo-3-azabicyclo[4.3.0]nonane-1-carboxylate (**39**-exo).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (1H, dd, *J* 2.4, 2.4 Hz), 5.19 (1H, dd, *J* 2.0, 2.0 Hz), 3.72 (3H, s), 3.145 (1H, d, *J* 7.2 Hz), 3.143 (1H, d, *J* 8.4 Hz), 2.98 (3H, s), 2.62–2.34 (3H, m), 1.79–1.62 (3H, m), 0.99 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 167.2, 147.7, 112.0, 64.9, 56.0, 53.0, 50.7, 35.2, 29.2, 29.1, 25.7, 16.3; IR (neat) 2953, 2929, 1740, 1645, 1227 cm^{-1}; HRMS (EI) *m*/*z* 237 $(M)^+$ calcd for $C_{13}H_{19}NO_3$ 237.1365, found 237.1361.

4.2.68. Methyl (1R,5R*,6R*)-3,5,9-trimethyl-2-oxo-3-azabicyclo [4.3.0]nona-8-ene-1-carboxylate (**39**-endo).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62–5.59 (1H, m), 3.73 (1H, dd, *J* 12.4, 4.4 Hz), 3.14 (1H, dd, *J* 12.4, 9.2 Hz), 2.99 (3H, s), 2.54 (1H, dddd, *J* 16.4, 8.0, 2.4, 2.4 Hz), 2.46 (1H, ddd, *J* 8.8, 8.0, 2.0 Hz), 2.11 (1H, dddd, *J* 16.4, 2.4, 2.0, 2.0 Hz), 1.88 (1H, ddd, *J* 2.4, 2.0, 2.0 Hz), 1.77 (1H, ddqd, *J* 9.2, 8.0, 6.8, 4.4 Hz), 1.03 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 167.4, 139.2, 128.5, 67.4, 54.8, 52.8, 50.2, 35.8, 35.5, 33.0, 17.4, 15.7; IR (neat) 2954, 2926, 1740, 1645, 1226 cm^{-1}; HRMS (EI) *m*/*z* 237 $(M)^+$ calcd for $C_{13}H_{19}NO_3$ 237.1365, found 237.1362.

4.2.69. Methyl (1S,5R*,6R*,9S*)-3,5,9-trimethyl-2-oxo-3-azabicyclo [4.3.0]nonane-1-carboxylate (**43**).* A mixture of **39** (151.3 mg, 0.637 mmol) in EtOH (2 mL) in the presence of 10% Pd/C (25 mg) was stirred under 1 atm of hydrogen. After 42 h, the reaction mixture was filtered through Celite® and the filtrate was concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 1:2 v/v) to provide **43** (151.0 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (3H, s), 3.06 (1H, dd, *J* 12.8, 11.2 Hz), 3.00 (3H, s), 2.97 (1H, dd, *J* 12.4, 4.0 Hz), 2.60 (1H, ddq, *J* 11.2, 6.8, 6.8 Hz), 2.47 (1H, ddd, *J* 10.0, 8.4, 8.4 Hz), 2.07 (1H, dddd, *J* 12.4, 7.2, 7.2, 2.4 Hz), 1.78 (1H, dddd, *J* 12.4, 6.8, 6.8, 2.4 Hz), 1.64–1.48 (2H, m), 1.24 (1H, dddd, *J* 12.4, 10.8, 8.8, 6.8 Hz), 1.15 (3H, d, *J* 6.8 Hz), 0.99 (3H, d, *J* 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 171.0, 62.1, 55.6, 52.4, 51.9, 43.1, 37.1, 35.6, 33.6, 31.6, 17.8, 16.4; IR (neat) 2953, 1730, 1651, 1455, 1223 cm^{-1}; HRMS (EI) *m*/*z* 239 $(M)^+$ calcd for $C_{13}H_{21}NO_3$ 239.1521, found 239.1510.

4.2.70. (1R,5R*,6R*,9S*)-3,5,9-Trimethyl-3-azabicyclo[4.3.0]nonan-2-one (**44**).* A stirred mixture of **43** (151.0 mg, 0.631 mmol) and LiCl (280 mg, 6.61 mmol) in DMSO (2.5 mL) and H_2O (0.5 mL) was heated at 160 °C for 4 h. After the mixture was cooled to rt, aqueous NaCl solution was added, the resulting mixture was extracted with EtOAc (three times). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 1:2 v/v) to provide **44** (104.7 mg, 91%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (1H, dd, *J* 12.4, 4.4 Hz), 3.00 (1H, dd, *J* 12.4, 9.6 Hz), 2.13 (1H, dd, *J* 9.2, 8.8 Hz), 2.11–1.93 (2H, m), 1.90–1.78 (2H, m), 1.63 (1H, ddqd, *J* 10.0, 9.2, 6.4, 4.0 Hz), 1.40 (1H, dddd, *J* 14.0, 8.4, 8.4, 5.6 Hz), 1.23 (3H, d, *J* 6.4 Hz), 1.17 (1H, dddd, *J* 12.4, 9.2, 8.4, 8.4 Hz), 0.94 (3H, d, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 55.9, 51.2, 45.2, 39.3, 34.9, 33.9, 32.9, 29.9, 21.1, 17.2; IR (neat) 2948, 1644 cm^{-1}; HRMS (EI) *m*/*z* 181 $(M)^+$ calcd for $C_{11}H_{19}NO$ 181.1467, found 181.1497.

*4.2.71. (±)-α-Skytanthine (**38**)*[18]. A stirred solution of **44** (96.8 mg, 0.534 mmol) in THF (10 mL) was cooled to 0 °C, and then $LiAlH_4$ (110 mg, 2.90 mmol) was added in one portion. The reaction mixture was allowed to warm to rt. After 14 h, aqueous saturated Na_2SO_4

solution (2.0 mL) was added dropwise at 0 °C, and then filtered and concentrated. The residue was subjected to column chromatography (CH_2Cl_2/MeOH/NH_4OH 100:5:1 v/v) to provide **38** (78.9 mg, 88%) as a colorless oil. The ^1H NMR data was in complete agreement with the reported values:[5] ^1H NMR (400 MHz, $CDCl_3$) δ 2.80 (1H, ddd, *J* 11.6, 1.6, 1.6 Hz), 2.65 (1H, dd, *J* 7.6, 1.6 Hz), 2.21 (3H, s), 2.09–2.00 (1H, m), 2.03 (1H, dd, *J* 11.6, 4.0 Hz), 1.92 (1H, dddd, *J* 12.8, 9.2, 9.2, 6.4 Hz), 1.70 (1H, dddd, *J* 13.2, 11.2, 6.4, 6.4 Hz), 1.52–1.33 (5H, m), 1.17 (1H, dddd, *J* 13.2, 10.8, 8.0, 5.2 Hz), 0.95 (3H, d, *J* 6.4 Hz), 0.81 (3H, d, *J* 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.7, 56.0, 48.4, 47.1, 45.1, 33.9, 33.1, 32.5, 27.7, 19.7, 18.1; IR (neat) 2950, 2869, 2776, 1462, 1141 cm^{-1}; HRMS (EI) *m*/*z* 167 $(M)^+$ calcd for $C_{11}H_{21}N$ 167.1674, found 167.1662.

The ^1H NMR data was in complete agreement with the reported values.[18e]

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